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# ORGANIC SYNTHESSES

# ORGANIC SYNTHESSES

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# ORGANIC SYNTHESSES

AN ANNUAL PUBLICATION OF SATISFACTORY  
METHODS FOR THE PREPARATION  
OF ORGANIC CHEMICALS

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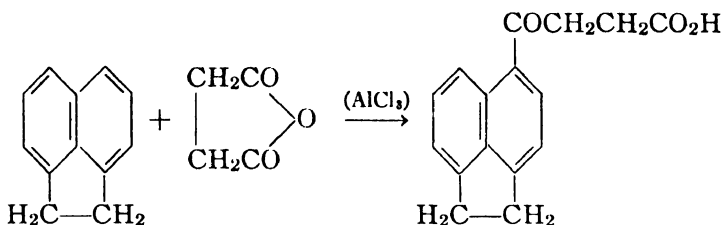
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# ORGANIC SYNTHESSES

## $\beta$ -(3-ACENAPHTHOYL)-PROPIONIC ACID

(Propionic Acid,  $\beta$ -3-Acenaphthenylcarbonyl-)



Submitted by L. F. FIESER

Checked by W. W. HARTMAN and A. WEISSBERGER

### 1. Procedure

In a 3-l. round-bottomed, three-necked flask (Note 1), 100 g. (0.65 mole) of pure acenaphthene (Note 2) and 72 g. (0.72 mole) of succinic anhydride (Org. Syn. **15**, 93) are dissolved by warming in 600 cc. of nitrobenzene. The flask is clamped in a large ice bath. Through the central opening is inserted a mercury-sealed mechanical stirrer. A second opening is connected to a gas trap (Org. Syn. **14**, 2) and also carries a thermometer, while the third is for the introduction of aluminum chloride. After the mixture has been cooled to about 0°, 195 g. (1.46 moles) of aluminum chloride is added in small portions in the course of one hour, keeping the temperature below 5°. Stirring is continued at 0° for four more hours, after which time the mixture is allowed to stand for at least twelve hours so that the ice melts and the clear red solution gradually comes to room temperature.

The flask is cooled by immersion in a slush of ice and water, and the addition compound is decomposed by adding gradually 200 g. of ice, 100 cc. of water, and 100 cc. of concentrated hydro-

chloric acid (this is best done under a hood). The keto acid separates in the form of a stiff, grayish-white paste. The solvent is removed by steam distillation, in which operation it is advisable to use a very rapid flow of steam together with an efficient condensing system, such as that illustrated (Fig. 1). The condensing flask shown need be no more than 1 l. in capacity, and

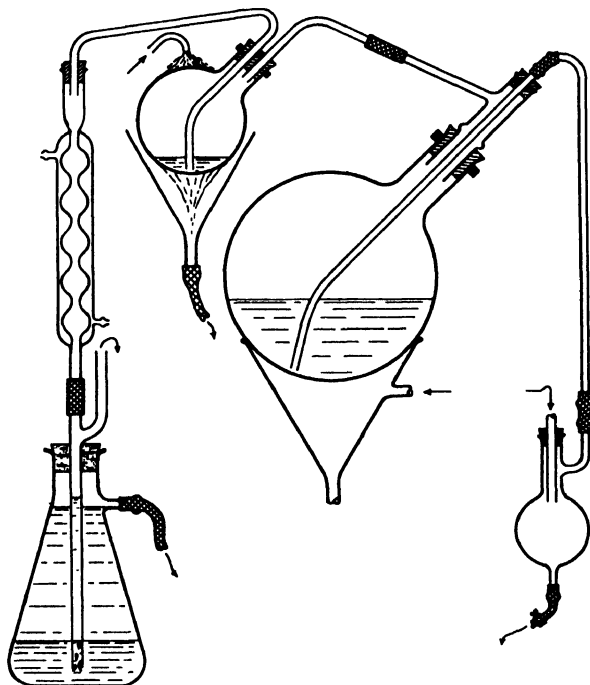


FIG. 1.

the exit tube should be centered at the bottom of this flask so that it can drain the contents completely. Some condensate ordinarily remains in the flask to serve as a vapor seal, a factor which adds greatly to the efficiency of condensation. For purposes of inspection, the flask can be emptied by diverting for a moment the stream of water to one side of the flask. The stoppers which are under pressure should be secured with wire. The distilling flask is heated to prevent too much condensation of steam (Note 3).

The bulk of the nitrobenzene comes over in about one and one-half hours, and the product then separates as a pasty mass which slowly disintegrates to a powder. During this process the elimination of nitrobenzene is very slow, but the steaming should be continued until only a few small lumps remain (four to five hours), although it is not necessary to remove every trace of solvent (Note 4). The mixture is cooled with tap water, the crude acid is filtered and returned to the flask, and 115 g. of sodium carbonate decahydrate is added, together with sufficient water to make the flask a little less than half full. The mixture is heated with shaking over a free flame until most of the solid has dissolved and the frothing has diminished. A few drops of capryl alcohol may be added to dissipate the froth. The dark brown solution is steam-distilled to eliminate the last traces of nitrobenzene (about one-half hour) and then filtered by suction from a very light residue. One hundred grams of sodium chloride is dissolved in the hot solution (volume, about 1.5 l.), which is then allowed to cool without disturbance. The sodium salt of  $\beta$ -(3-acenaphthoyl)-propionic acid separates as colorless, fibrous needles, while the isomeric 1-acid largely remains in solution (Note 5). The product is collected on a large Büchner funnel and washed free of the dark mother liquor with half-saturated sodium chloride solution (about 150 cc.), the combined filtrates (A) being set aside. The sodium salt is crystallized once more from boiling water (1-1.5 l.) (Note 6), using Norite if required, and adding 50 g. of sodium chloride to the hot filtered solution. The mother liquor (B) is again saved. The purified salt is dissolved in 1200 cc. of hot water and the solution is acidified. The free acid separates as a white powder in a very pure condition. The yield of  $\beta$ -(3-acenaphthoyl)-propionic acid melting at 206-208° with decomposition is 133 g. (81 per cent of the theoretical amount) (Note 7).

## 2. Notes

1. By using a flask suitable for steam distillation, the loss in time and material attending a transfer is avoided.
2. Suitable material is supplied by Reilly Tar and Chemical

Corporation, New York, or Gesellschaft für Teerverwertung, Duisburg-Meiderich, Germany.

3. As compared with the apparatus shown in Fig. 24 (Org. Syn. Coll. Vol. 1, 467), this arrangement requires a much smaller flask and yet offers unlimited capacity. It also enables the operator to observe more closely the character of the distillate.

4. If the flask fills up with condensed steam, it should be cooled, the contents filtered, and the product returned to the flask. The process of disintegration can be hastened by breaking up the lumps with a flattened stirring rod.

5. The small amount of isomeric 1-acid may be obtained from the mother liquors, A and B. The first of these on acidification gives a product which is dark and tarry, but which soon solidifies on being cooled and stirred. The material is dissolved in 1 l. of water containing 25–30 g. of sodium carbonate decahydrate, and the solution is boiled for one-half hour with Norite, filtered, cooled, and acidified. The product, which now solidifies at once and is lighter in color, is dried and combined with the material obtained by acidifying the second mother liquor, B (total amount, 23.9 g.). The crude mixture of acids is suspended in 170 cc. of cold methyl alcohol, 8.5 cc. of concentrated sulfuric acid is added, and the mixture is heated on the steam bath for about ten minutes, after which dissolution and esterification are complete. The dark product which crystallizes when the solution cools is largely the 1-ester, which is very much less soluble than the 3-ester. The 1-ester (13.1 g.) is washed free of acid; it crystallizes from ethyl alcohol with the use of decolorizing carbon in long needles melting at 126°; yield, 9 g. (Note 8). The ester is hydrolyzed by heating with 100 cc. of alcohol and 30 cc. of 25 per cent sodium hydroxide solution until dissolved; the solution is then diluted with water and acidified. The  $\beta$ -(1-acenaphthoyl)-propionic acid melts at 180° (crystallized from dilute alcohol, 181°) and weighs 8.4 g. (5 per cent) (Note 9).

6. If, owing to hydrolysis, the sodium salt fails to dissolve completely, alkali should be added as required.

7. The 3-acid crystallizes well from glacial acetic acid, alco-



hol, or xylene, but large volumes of solvent are required and there is no change in the melting point.

8. The 3-ester melts at  $89^{\circ}$ .

9. Ordinarily the mother liquors from the preparation and purification of 1-ester will be discarded, but a small additional quantity of the 3-acid may be obtained by concentrating these solutions, adding alkali to hydrolyze the ester, adding water, and acidifying. The precipitated material is purified by crystallizing the sodium salt twice, and from this 8 g. (5 per cent) of the pure 3-acid is obtained.

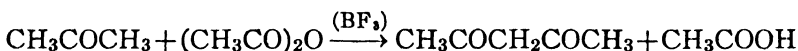
The ratio of 3-acid to 1-acid is dependent on the temperature, lower temperatures favoring the production of 3-acid. At  $-15^{\circ}$  the yield of 3-acid is 87 per cent, and of 1-acid, 5 per cent. At room temperature there is some increase in the proportion of the 1-acid formed, but the product is very dark and difficult to work up, and the total yield is lower even though the aluminum chloride is added in nitrobenzene solution.

### 3. Methods of Preparation

This procedure is based upon a study <sup>1</sup> of the method outlined in the patent literature.<sup>2</sup> The procedure is a general one and may be used for the condensation of succinic anhydride with naphthalene and with the mono- and dimethylnaphthalenes, although in no other case are the purification and separation of isomers so easily accomplished. In this particular type of condensation, as well as in certain other types of Friedel-Crafts reactions, nitrobenzene is far superior to the solvents which are more frequently employed. This is partly because of its great solvent power and partly because it forms a molecular compound with aluminum chloride, and so decreases the activity of the catalyst in promoting side reactions.

<sup>1</sup> Fieser, J. Am. Chem. Soc. **54**, 4350 (1932).

<sup>2</sup> Fr. pat. 636,065 [Chem. Zentr. (1928), I, 2751]; Swiss pat. 131,959 [Chem. Zentr. (1930), I, 1539]; U. S. pat. 1,759,111 [Chem. Zentr. (1930), II, 806]; Ger. pat. 376,635 [Frdl. **14**, 285 (1926)].

**ACETYLACETONE****(Diacetylmethane; 2,4-Pentanedione)****(A) (Boron Trifluoride Method)**

Submitted by C. E. DENOON, JR.

Checked by HOMER ADKINS and IVAN A. WOLFF.

**1. Procedure**

ONE HUNDRED AND SIXTEEN grams (2 moles) of acetone (Note 1) and 510 g. (5 moles) of reagent grade acetic anhydride are placed in a 2-l. three-necked flask and cooled in an ice-salt bath. One neck of the flask is stoppered, the second neck contains a tube for admitting boron trifluoride, and the third neck contains an outlet tube leading to an alkali trap to catch any unabsorbed boron trifluoride. Commercial grade boron trifluoride (Note 2) is passed through a Kjeldahl bulb, to prevent the reaction mixture from sucking back into the cylinder, and is then bubbled into the reaction mixture at such a rate that 500 g. is absorbed in about five hours (2 bubbles per second). The reaction mixture is poured into a solution of 800 g. of hydrated sodium acetate in 1600 cc. of water contained in a 5-l. flask. The mixture is then steam-distilled and the distillate collected in the following portions: 1000 cc., 500 cc., 500 cc., 400 cc.

A solution of reagent grade hydrated copper acetate is made by dissolving 240 g. of the salt in 3 l. of water at about 85° and filtering from any basic acetate. The copper salt of acetylacetone is then precipitated by adding 1400 cc. of the hot copper acetate solution to the first fraction of the acetylacetone, 700 cc. to the second, 500 cc. to the third, and 400 cc. to the fourth fraction. After standing for three hours, or better overnight, in a refrigerator the salt is filtered, washed once with water, and sucked dry. The salt is shaken in a separatory funnel with 800 cc. of 20 per cent sulfuric acid and 800 cc. of ether, and the ether

layer is removed. The aqueous layer is extracted with 400 cc. and then 200 cc. of ether. The combined extracts are dried with 250 g. of anhydrous sodium sulfate and the ether removed by distillation. The residue is distilled through a Widmer column (Note 3) and yields 160–170 g. of acetylacetone boiling at 134–136° (80–85 per cent of the theoretical amount based on the acetone).

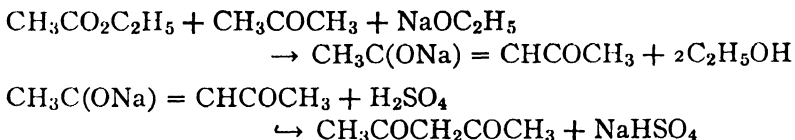
## 2. Notes

1. Acetone is preferably dried over anhydrous potassium carbonate or anhydrous calcium sulfate, followed by phosphorus pentoxide if a very dry product is required. Calcium chloride is commonly used (100–150 g. per liter), but this is less satisfactory since it combines chemically with acetone.<sup>1</sup> For this preparation the checkers used acetone that had been dried over calcium chloride, followed by distillation from phosphorus pentoxide.

2. Boron trifluoride may be purchased in cylinders from Harshaw Chemical Company, Cleveland, Ohio.

3. The Widmer column used contained a spiral 15 cm. in length, 13 mm. in diameter, with 15 turns of the helix.

### (B) (Sodium Ethoxide Method)



Submitted by HOMER ADKINS and JAMES L. RAINEY.

Checked by R. L. SHRINER and NEIL S. MOON.

## 1. Procedure

SIXTY-NINE grams (3 gram atoms) of sodium, from which all the oxide coating has been cut away, and 400 cc. of dry xylene (Note 1) are placed in a 1-l. round-bottomed flask and heated until the sodium is melted. The flask is closed with a rubber

<sup>1</sup> Bagster, J. Chem. Soc. (1917), 494.

stopper (Note 2) and the sodium is finely powdered by vigorous shaking. The contents of the flask are transferred to a 3-l. three-necked flask, and the xylene decanted. The sodium is washed with two 100-cc. portions of anhydrous ether (Note 3) by decantation. One liter of anhydrous ether is added, and the flask is placed on a steam bath and fitted with a condenser, Hershberg stirrer (Org. Syn. 17, 31), and a 250-cc. dropping funnel. The condenser and dropping funnel are protected by drying tubes containing absorbent cotton (Note 4). One hundred and thirty-eight grams (175 cc., 3 moles) of anhydrous ethyl alcohol is placed in the dropping funnel, and the stirrer is started. The alcohol is dropped in over a period of two to three hours with gentle refluxing. The reaction mixture is refluxed with stirring for six hours (Note 5) after the addition of the alcohol. The stirrer is stopped, the condenser turned downward, and the ether distilled as completely as possible from the steam bath (Note 6).

The condenser is again arranged for refluxing, and 1.2 l. of ethyl acetate (Note 7) is added to the warm sodium ethoxide through the separatory funnel as rapidly as possible. The stirrer is started immediately, and 174 g. (220 cc., 3 moles) of acetone (Note 1, p. 7) is dropped in over a period of fifteen to twenty minutes, refluxing being maintained by heating if necessary. Addition of the acetone must be started as soon as the ethyl acetate has been added. During the addition the solution becomes quite red, and then the mixture turns brown (Note 8). The mixture is refluxed for one hour; the stirrer is then stopped and the contents of the flask allowed to stand at room temperature for twelve hours, during which time crystals of the sodium salt separate.

The liquid layer is decanted into a 5-l. flask and the sodium salt of the diketone is dissolved and washed into the flask with 2.5 l. of ice water. After the salt is dissolved, the ester layer is separated as soon as possible (Note 9). The water layer is extracted twice with 300-cc. portions of ether and the ether extract discarded. To the water solution is added ice-cold dilute sulfuric acid (150 g. of concentrated sulfuric acid and 400 g. of cracked ice) until the solution is just acid to litmus. The dike-

tone is extracted from the solution with four 300-cc. portions of ether. The combined ether extracts are dried for twenty-four hours over 60 g. of anhydrous sodium sulfate in the icebox. The ether solution is decanted into a 2-l. round-bottomed flask and the sodium sulfate extracted with 100 cc. of anhydrous ether. This extract is added to the ether solution and the ether distilled by means of a steam bath. The residue is transferred to a 500-cc. flask, rinsing with a little ether, and distilled through a Widmer column, the portion boiling between  $130^{\circ}$  and  $139^{\circ}$  being collected. This fraction is dried over 5 g. of anhydrous potassium carbonate for one hour and, after removing the carbonate, redistilled through the Widmer column. The portion boiling at  $134-136^{\circ}$  is collected and amounts to 115-136 g. (38-45 per cent of the theoretical amount based on the acetone).

## 2. Notes

1. The xylene is dried by distillation from sodium.
2. Rubber stoppers should be used throughout, including the drying of reagents, as corks contain some moisture. The stoppers should be boiled in 10 per cent sodium hydroxide solution for two hours, thoroughly washed with dilute acetic acid, and dried.
3. Commercial anhydrous ethyl ether and ethyl alcohol are satisfactory. If these are unavailable, the ether should be purified as for use in the Grignard reaction and the alcohol as described in *Org. Syn. Coll. Vol. 1*, 244.
4. Absorbent cotton is an excellent drying agent and more convenient for drying tubes than anhydrous calcium chloride.<sup>2</sup> It is possible to keep maleic anhydride in a flask closed only by a plug of absorbent cotton, for three weeks without appreciable change in the titration value (F. P. Pingert, private communication).
5. The period of heating varies somewhat with the size of the powdered sodium. Almost all the sodium should be used up before removal of the ether. However, a few small pieces do no harm.
6. The success of the reaction depends upon the quality of the sodium ethoxide used. The product at this point should be white

<sup>2</sup> Obermiller and Goertz, *Z. physik. Chem.* **109**, 162 (1924).

and very finely divided. All moisture must be excluded during its preparation in order to avoid the formation of sodium hydroxide, which markedly lowers the yield.

7. The ethyl acetate is allowed to stand over calcium chloride for two days, with occasional shaking. The calcium chloride is removed by filtration, and the ester is allowed to stand over phosphorus pentoxide several hours. It is then distilled directly from the phosphorus pentoxide.

8. After about half of the acetone has been added, the mixture usually sets to a solid mass. The stirrer is turned by hand and the addition of acetone continued. In a few minutes the mass can again be stirred.

9. The ethyl acetate layer is washed with water, sodium bisulfite solution, saturated calcium chloride solution, and again with water. It is further purified as in Note 6, giving 316–400 g. of recovered ester. The amount of recovered ester depends somewhat upon the length of time the two layers are allowed to remain in contact before separating.

### 3. Methods of Preparation

Acetylacetone has been prepared by the reaction of acetyl chloride with aluminum chloride followed by hydrolysis,<sup>3</sup> and by the condensation of acetone with ethyl acetate under the influence of sodium,<sup>4</sup> sodamide,<sup>5</sup> and sodium ethoxide,<sup>5,6,7</sup> and by the reaction of acetone and acetic anhydride in the presence of boron trifluoride.<sup>8</sup>

<sup>3</sup> Combes, *Ann. chim. phys.* (6) **12**, 207 (1887).

<sup>4</sup> Claisen, *Ann.* **277**, 168 (1893).

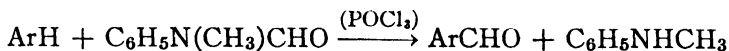
<sup>5</sup> Claisen, *Ber.* **38**, 695 (1905).

<sup>6</sup> Claisen and Ehrhardt, *ibid.* **22**, 1010 (1889).

<sup>7</sup> Sprague, Beckham, and Adkins, *J. Am. Chem. Soc.* **56**, 2665 (1934)

<sup>8</sup> Meerwein and Vossen, *J. prakt. Chem.* **141**, 149 (1934).

## 9-ANTHRALDEHYDE; 2-ETHOXY-1-NAPHTHALDEHYDE



Submitted by (A) L. F. FIESER, J. L. HARTWELL, and J. E. JONES;

(B) J. H. WOOD and R. W. BOST.

Checked by C. F. H. ALLEN and J. VAN ALLAN.

## 1. Procedure

(A) *9-Anthraldehyde*.—In a 2-l. round-bottomed flask fitted with a mechanical stirrer and reflux condenser are placed 35 g. (32 cc., 0.26 mole) of methylformanilide (p. 66), 35 g. (21 cc., 0.23 mole) of phosphorus oxychloride, 20 cc. of *o*-dichlorobenzene, and 22.5 g. (0.13 mole) of anthracene (Note 1). This is heated on the steam bath, with stirring, to 90–95° over a period of twenty minutes; the anthracene dissolves during this time to give a deep red solution, and hydrogen chloride is evolved (Note 2). The heating is continued for one hour (Note 3), after which a solution of 140 g. of crystalline sodium acetate in 250 cc. of water (Note 4) is added to the cooled mixture, and the *o*-dichlorobenzene and most of the methylaniline are rapidly distilled with steam (fifteen to twenty minutes). The residual reddish oil solidifies on cooling. The solid residue is broken up, and, after decanting the aqueous liquor through a Büchner funnel, it is washed by decantation with two 100-cc. portions of 6 *N* hydrochloric acid to remove amine, and then thoroughly with water (1000–1200 cc.). The crude solid (22–24 g., m. p. 97–101°) is recrystallized from 50 cc. of hot glacial acetic acid; when cold, the bright yellow aldehyde is filtered by suction and washed on the filter with 30 cc. of methanol (Note 5). The yield is 20–22 g. (77–84 per cent of the theoretical amount) and the melting point is 104.5–105° (Note 6).

(B) *2-Ethoxy-1-naphthaldehyde*.—A mixture of 45 g. (0.33 mole) of methylformanilide (p. 66), 51 g. (0.33 mole) of phosphorus oxychloride, and 43 g. (0.25 mole) of  $\beta$ -naphthyl ethyl ether in a 500-cc. round-bottomed flask provided with an air con-

denser (Note 2) is heated on a steam bath for six hours. The hot mixture is then poured in a thin stream into 700 cc. of cold water with very vigorous stirring, to avoid the formation of large lumps (Note 7); the aldehyde separates in a granular condition. It is filtered by suction and washed thoroughly, using 1 l. of water. Without drying, the crude aldehyde is dissolved in 450 cc. of alcohol and decolorized by the addition of 4 g. of Norite, boiling for fifteen minutes, and filtering hot (Note 8), using a double filter paper. The filtrate is cooled and the product is collected on a filter and washed with 40 cc. of cold alcohol; it crystallizes in pale yellow needles, m.p. 111–112°. The yield is 37–42 g. (74–84 per cent of the theoretical amount).

## 2. Notes

1. The yield and purity of the anthraldehyde depend on the quality of the hydrocarbon. The figures given are attained only if the anthracene melts at 213° or higher. With anthracene, m.p. 208–210°, the yield is 19–20 g., m.p. 103–104° (Note 6).

2. The reaction may be carried on in a hood, or a gas trap (Org. Syn. 14, 2) may be used.

3. When run on a fourfold scale, the time of heating should be extended to two hours. Prolonged heating leads to the formation of tars.

4. Sodium acetate appears to decompose a product of the condensation of methylaniline with phosphorus oxyhalides; substances other than the aldehyde are largely retained in the sodium acetate solution.

5. A brighter-colored product is secured by this wash.

6. The aldehyde also exists in a low-melting form, m.p. 98.5–99.5°, and occasionally this form is obtained from the reaction. It is less stable than the high-melting form, into which it is easily converted by seeding.

7. Care must be exercised to prevent the reaction product from lumping upon being poured into water. If this happens, decomposition by the water is slow and subsequent purification is more difficult. Any lumps which are formed should be broken



up and the reaction mixture should then be permitted to stand overnight in contact with the water. The flask in which the reaction is carried out is also filled with water to decompose the product adhering to the walls. This is purified with the rest.

8. A heated funnel is desirable. Some of the product usually crystallizes during the filtration.

### 3. Methods of Preparation

This aldehyde synthesis is applicable to compounds of the aromatic series having a labile hydrogen atom (phenyl ethers,<sup>1</sup> naphthols,<sup>2</sup> dialkylanilines,<sup>3,4</sup> naphthostyryl,<sup>2</sup> anthrones<sup>2</sup>) and to certain hydrocarbons of requisite reactivity (anthracene,<sup>5,6</sup> 1,2-benzanthracene,<sup>6</sup> 3,4-benzpyrene,<sup>3,7</sup> pyrene,<sup>8</sup> styrene,<sup>9</sup> and  $\alpha, \alpha$ -diarylethylenes<sup>9</sup>). With polynuclear hydrocarbons the best results are secured by the use of a solvent such as *o*-dichlorobenzene. 9-Anthraldehyde has also been prepared by the action of hydrogen cyanide and aluminum chloride on anthracene in chlorobenzene.<sup>10</sup>

With liquid or low-melting ethers no solvent is required. 2-Ethoxy-1-naphthaldehyde has also been prepared by ethylation of the hydroxy compound,<sup>11</sup> and from  $\beta$ -naphthyl ethyl ether by the Gattermann reaction.<sup>12</sup>

<sup>1</sup> Wood and Bost, J. Am. Chem. Soc. **59**, 1722 (1937).

<sup>2</sup> Ger. pat. 514,415 [Frdl. **17**<sup>1</sup>, 564 (1932)].

<sup>3</sup> Vilsmeier and Haak, Ber. **60**, 119 (1927).

<sup>4</sup> Ger. pat. 547,108 [Frdl. **18**<sup>2</sup>, 2973 (1933)].

<sup>5</sup> Ger. pat. 519,444 [Frdl. **17**<sup>1</sup>, 565 (1932)].

<sup>6</sup> Fieser and Hartwell, J. Am. Chem. Soc. **60**, 2556 (1938).

<sup>7</sup> Fieser and Hershberg, *ibid.* **60**, 2547 (1938).

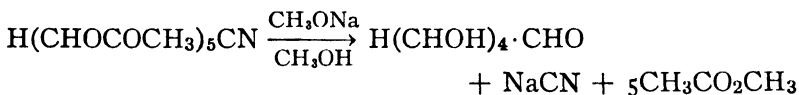
<sup>8</sup> Vollmann, Becker, Corell, and Streeck, Ann. **531**, 1 (1937).

<sup>9</sup> Brit. pat. 504,125 [C. A. **33**, 7313 (1939)].

<sup>10</sup> Hinkel, Ayling, and Beynon, J. Chem. Soc. (1936), 344.

<sup>11</sup> Bartsch, Ber. **36**, 1975 (1903).

<sup>12</sup> Gattermann, Ann. **357**, 367 (1907).

***d*-ARABINOSE**

Submitted by GÉZA BRAUN.

Checked by H. T. CLARKE and S. M. NAGY.

**1. Procedure**

A SOLUTION of 100 g. (0.26 mole) of pentaacetyl glucononitrile (p. 74) in 150 cc. of chloroform in a 1-l. Erlenmeyer flask is chilled to  $-12^\circ$ . A chilled ( $-12^\circ$ ) solution of 16 g. (0.7 gram atom) of sodium in 250 cc. of anhydrous methyl alcohol is added with continual shaking and chilling to the chloroform solution of the nitrile. The mixture soon solidifies to a pale yellow, gelatinous mass. After ten minutes at  $-12^\circ$  this is broken up with a heavy glass rod and dissolved in 600 cc. of a suspension of ice in water. The resulting solution is acidified with an ice-cold mixture of 33 g. (18 cc., 0.32 mole) of 95 per cent sulfuric acid, 5 cc. of acetic acid, and 45 g. of ice. The aqueous layer is separated, washed once with 50 cc. of chloroform, and evaporated without delay (Note 1) under reduced pressure. The residual heavy syrup is dissolved in 300 cc. of water and again evaporated as completely as possible under reduced pressure, in order to remove residual hydrogen cyanide (Note 2). The highly viscous residue, which contains some crystals of sodium sulfate, is dissolved in 500 cc. of hot methyl alcohol. After about ten minutes the sodium sulfate is filtered with suction and washed with two 25-cc. portions of methyl alcohol. The filtrate is concentrated under reduced pressure at  $40^\circ$  to a heavy syrup which is poured while warm into a 200-cc. Erlenmeyer flask. The distilling flask is rinsed twice with 20-cc. portions of hot ethyl alcohol, and this rinse is added to the filtrate. The resulting alcohol solution soon begins to deposit crystals of arabinose; it is stirred by hand during the crystallization and gradually diluted with more alcohol until 100 cc. in all has been added during the course

of an hour. The mixture is allowed to stand for four to five hours; the crystals are then filtered, washed with two 25-cc. portions of ethyl alcohol, and dried at 40°. The yield of colorless *d*-arabinose, m.p. 158–158.5°,  $[\alpha]_D^{20} - 105^\circ$  (final value), is 23.5–26.3 g. (61–68 per cent of the theoretical amount) (Note 3).

## 2. Notes

1. After the reaction mixture has been dissolved in water and acidified, the hydrogen cyanide should be removed as soon as possible, for the arabinose tends to react with it even in dilute solution.

2. A slightly higher yield of crystalline arabinose is obtainable by removing the hydrogen cyanide with silver acetate. The procedure then consists in acidifying with acetic acid in place of sulfuric acid, adding an excess of silver acetate, shaking for an hour, filtering, saturating with hydrogen sulfide, again filtering, and adding sulfuric acid as indicated above. The rest of the procedure is the same. The yield of crystalline arabinose so obtained is 27.1 g. (70 per cent of the theoretical amount).

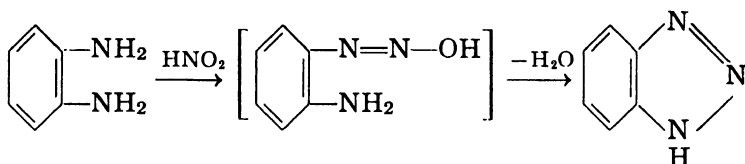
3. A further quantity of arabinose may be isolated from the mother liquors by the use of diphenylhydrazine: to a solution of 22 g. of diphenylhydrazine hydrochloride in 100 cc. of absolute methyl alcohol is added a solution of 3.3 g. of sodium in 50 cc. of methyl alcohol. After fifteen minutes' standing the sodium chloride is removed by filtration and washed with methyl alcohol. The filtrate, which contains approximately 18 g. of free diphenylhydrazine, is added to the alcoholic mother liquor from the arabinose and the mixture is inoculated with diphenylhydrazone prepared from some of the crystalline arabinose. The mixture is allowed to stand overnight, and the crystalline diphenylhydrazone is filtered, washed with 95 per cent ethyl alcohol, and dried in a vacuum desiccator. In a preparation in which the yield of crystalline arabinose had been 23.5 g., the yield of diphenylhydrazone was 16.5 g., corresponding to 7.8 g. of the sugar. Arabinose can be recovered from the diphenylhydrazone by treatment with formaldehyde in aqueous solution. In view of the

high cost of diphenylhydrazine, however, it is doubtful whether its use for this purpose is profitable.

### 3. Methods of Preparation

*d*-Arabinose was first prepared by Wohl,<sup>1</sup> by treating pentaacetyl glucononitrile with ammoniacal silver nitrate. It has also been obtained from *d*-gluconic acid in various ways: by oxidation of the calcium salt by means of hydrogen peroxide in the presence of ferric acetate;<sup>2</sup> by boiling an aqueous solution of the mercuric salt;<sup>3</sup> by electrolysis;<sup>4</sup> by the action of sodium hypochlorite upon the amide.<sup>5</sup> The present method, developed by Zemplén and Kiss,<sup>6</sup> furnishes better yields than that of Wohl.

### 1,2,3-BENZOTRIAZOLE



Submitted by R. E. DAMSCHRODER and W. D. PETERSON.

Checked by W. E. BACHMANN and W. S. STRUVE.

### 1. Procedure

IN a 1-l. beaker are placed 108 g. (1 mole) of *o*-phenylenediamine (Org. Syn. 19, 70), 120 g. (115 cc., 2 moles) of glacial acetic acid, and 300 cc. of water. By warming the mixture slightly a clear solution is obtained. The beaker is placed in ice water and the contents cooled to 5°. As soon as this temperature is reached, a cold solution of 75 g. (1.09 moles) of sodium nitrite

<sup>1</sup> Wohl, Ber. 26, 730 (1893).

<sup>2</sup> Ruff, ibid. 32, 550 (1899).

<sup>3</sup> Guerbet, Bull. soc. chim. (4) 3, 427 (1908).

<sup>4</sup> Neuberg, Biochem. Z. 7, 527 (1908).

<sup>5</sup> Weermann, Rec. trav. chim. 37, 16 (1917).

<sup>6</sup> Zemplén and Kiss, Ber. 60, 165 (1917).

in 120 cc. of water is added all at once, the mixture being stirred with a glass rod or by a slow mechanical stirrer. The reaction mixture turns a dark green color, and the temperature rises rapidly to 70–80° (Note 1). The color of the solution changes to a clear orange-red. The beaker is now removed from the cooling bath and the contents allowed to stand for one hour; as the solution cools, the benzotriazole separates as an oil. The beaker is then packed in ice, and the mixture is stirred until it sets to a solid mass. After being kept cold for three hours, the solid is collected on a Büchner funnel, washed with 200 cc. of ice water, and sucked as dry as possible under a rubber dam. The tan-colored product, after drying at 45–50° overnight, weighs 110–116 g.

The crude benzotriazole is placed in a 200-cc. modified Claisen flask (Org. Syn. Coll. Vol. 1, 125) and distilled under reduced pressure (Note 2). The yield of white solid (yellow cast) boiling at 201–204° at 15 mm. or 156–159° at 2 mm. is 92–99 g. The product in the receiver is melted over a luminous flame and poured into 250 cc. of benzene. The clear solution is stirred until crystallization sets in; after being chilled for two hours, the product is filtered on a Büchner funnel. The colorless benzotriazole weighs 90–97 g. (75–81 per cent of the theoretical amount) (Note 3) and melts at 96–97°.

## 2. Notes

1. Too efficient cooling and stirring are to be avoided. It is essential that the temperature rise to 80°. Too rapid cooling after this temperature has been reached results in lower yields. With runs one-tenth this size it is advisable to remove the mixture from the cooling bath as soon as the sodium nitrite has been added in order to ensure the rise in temperature.

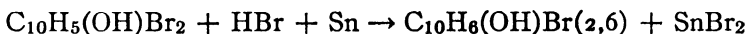
2. The crude product can be purified by repeated crystallizations from benzene or water. Greater losses accompany this tedious method of purification than a single distillation.

3. The submitters report that runs of double this size can be made with equally good results.

### 3. Methods of Preparation

1,2,3-Benzotriazole has been prepared directly by the action of nitrous acid on *o*-phenylenediamine<sup>1</sup> and by the hydrolysis of an acylated or aroylated benzotriazole which has been previously prepared by the action of nitrous acid on the corresponding mono acylated or aroylated *o*-phenylenediamine.<sup>2,3,4</sup> The above procedure is the direct method and gives better over-all yields than the methods involving several intermediate steps. Most methods described in the literature employ mineral acid. Acetic acid is much more satisfactory.

### 6-BROMO-2-NAPHTHOL



Submitted by C. FREDERICK KOELSCH.

Checked by W. E. BACHMANN and S. KUSHNER.

#### 1. Procedure

IN a 3-l. round-bottomed flask fitted with a dropping funnel and a reflux condenser (Note 1) are placed 144 g. (1 mole) of  $\beta$ -naphthol and 400 cc. of glacial acetic acid. Through the dropping funnel is then added a solution of 320 g. (2 moles) of bromine in 100 cc. of acetic acid. The flask is shaken gently during the addition, which requires fifteen to thirty minutes. The  $\beta$ -naphthol dissolves during this period and heat is evolved; the mixture is cooled somewhat towards the end of the addition to

<sup>1</sup> Ladenburg, Ber. 9, 219 (1876).

<sup>2</sup> Bell and Kenyon, J. Chem. Soc. (1926), 954.

<sup>3</sup> Fieser and Martin, J. Am. Chem. Soc. 57, 1838 (1935).

<sup>4</sup> Charrier and Beretta, Gazz. chim. ital. 51, (Part 2), 267 (1921).

avoid excessive loss of hydrogen bromide. One hundred cubic centimeters of water is then added, and the mixture is heated to boiling. It is then cooled to  $100^{\circ}$ , 25 g. of mossy tin is added (Note 2), and boiling is continued until the metal is dissolved. A second portion of 25 g. of tin is then added and dissolved by boiling, and finally a third portion of 100 g. (a total of 150 g., 1.27 gram atoms) of tin is introduced. The mixture is boiled for three hours, cooled to  $50^{\circ}$ , and filtered with suction. The crystalline tin salts which are thus removed are washed on the funnel with 100 cc. of cold acetic acid, the washings being added to the main portion of the filtrate.

This filtrate is stirred into 3 l. of cold water; the 6-bromo-2-naphthol which is precipitated is filtered with suction, removed from the funnel, and washed by stirring with 1 l. of cold water. After filtering again and drying at  $100^{\circ}$  there is obtained 214–223 g. (96–100 per cent of the theoretical amount) of 6-bromo-2-naphthol. This crude product, which is pink and melts at  $123-127^{\circ}$ , contains some tin but is pure enough for most purposes.

A white product is obtained by vacuum distillation followed by crystallization of the crude product. Twenty-five grams of the crude substance on distillation (Note 3) gives 20 to 24 g. of distillate boiling at  $200-205^{\circ}$  at 20 mm., and when this is crystallized from a mixture of 75 cc. of acetic acid and 150 cc. of water it gives 17.5 to 22.5 g. of 6-bromo-2-naphthol which melts at  $127-129^{\circ}$ .

## 2. Notes

1. An all-glass apparatus is of considerable advantage. If this is not available, the cork is covered with lead foil.

2. The reflux condenser is removed in order to add the tin, but it should be held in readiness so that it can be replaced quickly. The first two portions of tin react vigorously, and solution of the metal is accompanied by the evolution of hydrogen and the loss of some hydrogen bromide.

3. For the distillation a sausage flask or two-bulb flask<sup>1</sup> (Fig. 2) is employed.

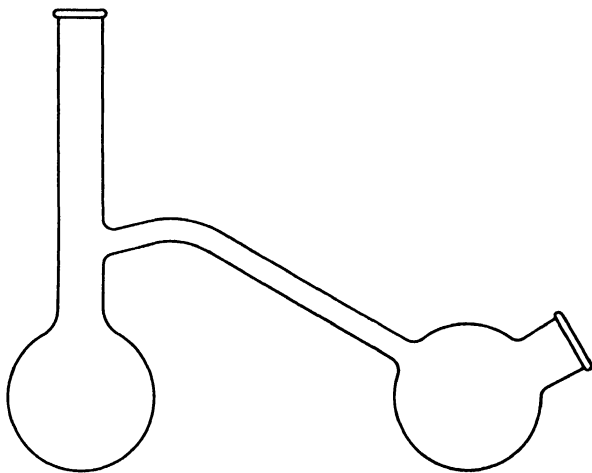


FIG. 2.

### 3. Methods of Preparation

6-Bromo-2-naphthol has been prepared by the reduction of 1,6-dibromo-2-naphthol with hydriodic acid,<sup>2</sup> with tin and hydrochloric acid,<sup>3</sup> or with stannous chloride and hydrochloric acid in aqueous alcohol<sup>3</sup> or in aqueous acetic acid.<sup>4</sup>

<sup>1</sup> Fieser, "Experiments in Organic Chemistry," p. 246, Heath and Co., New York, 1935.

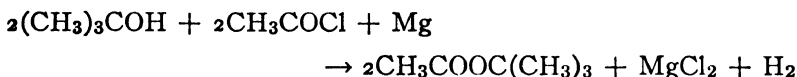
<sup>2</sup> Armstrong, Chem. News **74**, 302 (1897).

<sup>3</sup> Franzen and Staubel, J. prakt. Chem. (2) **103**, 369 (1922); Fries and Schimmelschmidt, Ber. **58**, 2840 (1925).

<sup>4</sup> Fries and Schimmelschmidt, Ann. **484**, 293 (1930).



*tert.*-BUTYL ACETATE



Submitted by A. SPASSOW.

Checked by W. E. BACHMANN and J. KORMAN.

### 1. Procedure

IN a 1-l. round-bottomed flask are placed 12 g. (0.5 gram atom) of magnesium powder, 37 g. (0.5 mole) of *tert.*-butyl alcohol, and 100 g. of anhydrous ether (Note 1). The flask is fitted with an addition tube, one arm of which bears a reflux condenser, and the other arm a dropping funnel. While the mixture is being shaken by hand, a solution of 55 g. (0.7 mole) of acetyl chloride (Note 2) in 50 g. of anhydrous ether is added dropwise (Note 3). A lively reaction gradually ensues with evolution of hydrogen, mixed with ether vapor and a little hydrogen chloride (Note 4). After all the acetyl chloride has been added, the reaction mixture is allowed to stand in a pan of cold water for one hour (Note 5). After another hour at room temperature the mixture is warmed in a water bath at 40–45° for one-half hour in order to complete the reaction.

The solid reaction product is cooled in ice water and decomposed by addition of an ice-cold solution of 20 g. of potassium carbonate in 250 cc. of water, cooling being continued throughout (Note 6). The mixture is extracted three times with 35-cc. portions of ether; the ether extract is dried over calcium chloride and then distilled (Note 7). The ester is obtained from the fraction boiling at 85–98° by fractional distillation by means of a good column (Note 8). The purified ester boils at 95–97° at 740 mm. and weighs 37–45 g. (45–55 per cent of the theoretical amount).

### 2. Notes

1. The *tert.*-butyl alcohol must be completely anhydrous. It was dried over sodium and distilled from sodium just before use. The ether was likewise dried over sodium.

2. The acetyl chloride was distilled before use.
3. The addition of the acetyl chloride requires about fifteen minutes. After addition of about two-thirds of the acid chloride, the reaction mixture rapidly becomes semisolid.
4. The course of the esterification is best followed by the evolution of the hydrogen, the latter being led by means of a tube from the top of the condenser through a wash bottle containing a small amount of water. A moderate rate of reaction is obtained throughout by judicious immersion of the reaction flask in a pan of cold water.
5. After one-half hour the reaction becomes more lively and the mixture more fluid.
6. The potassium carbonate solution is added all at once. The carbon dioxide which is evolved does not interfere with the extraction of the ester.
7. Since the ester is quite volatile, the ether is distilled off through a 60-cm. Vigreux column. The distillation is interrupted at 40°, and a 40-cm. column is employed. A fraction boiling up to 85° and one boiling from 85° to 98° are collected. The first fraction, which contains considerable amounts of the ester, is redistilled, and the portion boiling above 85° is added to the second fraction. The fraction boiling from 85° to 98° weighs 43–48 g.
8. A 40-cm. Vigreux or Widmer column is used for this distillation. The fore-run is redistilled from the same flask.

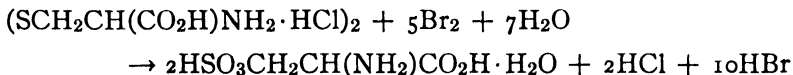
### 3. Methods of Preparation

*tert.*-Butyl acetate has been prepared from *tert.*-butyl alcohol and acetic anhydride in the presence of anhydrous sodium acetate<sup>1</sup> and from the alcohol and acetic anhydride in the presence of a small amount of zinc dust.<sup>2</sup>

<sup>1</sup> Tronow and Ssibgatullin, Ber. **62**, 2850 (1929).

<sup>2</sup> Norris and Rigby, J. Am. Chem. Soc. **54**, 2097 (1932).

## CYSTEIC ACID MONOHYDRATE



Submitted by H. T. CLARKE.

Checked by HENRY GILMAN and H. J. HARWOOD.

## 1. Procedure

To a solution of 24 g. (0.1 mole) of cystine (Org. Syn. Coll. Vol. 1, 188) in a cold mixture of 150 cc. of water and 50 cc. of concentrated hydrochloric acid is added, dropwise, 80 g. (25 cc., 0.5 mole) of commercial bromine, with occasional stirring, during forty minutes. The temperature of the mixture rises to about 60°. The resulting solution, which contains a little unreduced bromine, is then evaporated under reduced pressure on a steam bath. The dark-colored, crystalline residue is dissolved in 100 cc. of distilled water and filtered from a small quantity of amorphous, insoluble matter. The filtrate is concentrated by evaporation on a water bath to 65 cc. and allowed to crystallize by standing overnight in a refrigerator. The crystals are filtered with suction and washed well with about 100 cc. of 95 per cent ethyl alcohol in several portions, the washings being collected separately. The crystals are dried *in vacuo* over phosphorus pentoxide. A second crop is obtained by diluting the washings with an equal volume of water, evaporating until free of alcohol (Note 1), adding the residue to the mother liquor, and evaporating the combined solution to dryness on the water bath. The residue is dissolved in 30–40 cc. of water, decolorized with 0.5–1.0 g. of charcoal, concentrated to 15 cc., and, when cold, treated with 30 cc. of 95 per cent ethyl alcohol. The crystals so formed are collected, washed with ethyl alcohol, and dried as before (Note 2). The total yield is 30.5–33.5 g. of pure cysteic acid monohydrate (81–90 per cent of the theoretical amount). It melts, with vigorous evolution of gas, at 278° (289° corr.) (Note 3), and shows the rotation  $[\alpha]_{546}^{24} + 9.36^\circ$  (6 per cent in water).

## 2. Notes

1. Cysteic acid appears to esterify readily on warming with ethyl alcohol, but the resulting ester is rapidly hydrolyzed by warming with dilute mineral acid.

2. The final mother liquors, on evaporation to dryness, yield 2-3 g. of a light brown, amorphous product which is readily soluble in water but insoluble in 95 per cent alcohol. In concentrated hydrobromic acid this by-product forms a dark solution, the color of which is discharged on dilution with water.

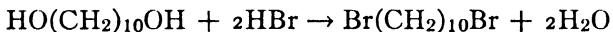
3. The decomposition point of  $278^{\circ}$  is obtained by placing the capillary in a bath already heated to  $260-270^{\circ}$ . If the sample is slowly heated, starting at room temperature, a decomposition point of  $257-258^{\circ}$  is observed.

## 3. Methods of Preparation

The most convenient oxidant for the preparation of cysteic acid from cystine is aqueous bromine.<sup>1</sup> Iodine<sup>2</sup> and hydrogen peroxide<sup>3</sup> also bring about the reaction, but with both substances some of the sulfur is split off as sulfuric acid.

## DECAMETHYLENE BROMIDE

(Decane, 1,10-Dibromo-)



Submitted by W. L. McEWEN.

Checked by REYNOLD C. FUSON and E. A. CLEVELAND.

## 1. Procedure

A 2-l. three-necked flask, supported in an oil bath, is fitted with a mechanical stirrer and an inlet tube which reaches almos

<sup>1</sup> Friedmann, Beitr. Chem. Physiol. u. Pathol. **3**, 1 (1903).

<sup>2</sup> Yamazaki, J. Biochem. (Japan) **12**, 207 (1930); Shinohara, J. Biol. Chem. **96**, 285 (1932).

<sup>3</sup> Schöberl, Z. physiol. Chem. **216**, 193 (1933).

to the bottom of the flask. In it is placed 696 g. (4 moles) of decamethylene glycol (Org. Syn. 14, 20), and, after the oil bath is heated to 95–100°, a rapid stream of dry hydrogen bromide (Org. Syn. 15, 35) is introduced, with stirring. When the mixture becomes saturated with the gas, as shown by vigorous fuming at the open neck of the flask (Note 1), the temperature of the oil bath is raised to 135° and a slow current of hydrogen bromide is passed in for six hours (Note 2).

After cooling, the crude product is transferred to a separatory funnel and the lower aqueous layer is drawn off and discarded. The upper layer is washed once with an equal volume of warm water, and then with successive portions of 10 per cent sodium carbonate solution until all acid has been removed. It is then washed once with warm water which is separated as completely as possible (Note 3). The product thus washed is distilled from a Claisen flask under reduced pressure. The first few drops of distillate containing some water are discarded: the main fraction distills at 139–142° at 2 mm. The yield is 1080 g. (90 per cent of the theoretical amount) (Note 4).

## 2. Notes

1. In larger runs it is advantageous to stop the stirrer and gas stream at this point and allow the lower aqueous layer to separate, after which it is siphoned out.

2. The total quantity of bromine used is about 950 g.

3. If difficulty is encountered with separation of layers in washing, the substance may be dissolved in an equal volume of ether.

4. This yield was almost invariably obtained by the submitter, who used quantities of glycol varying from 150 g. to 2000 g.

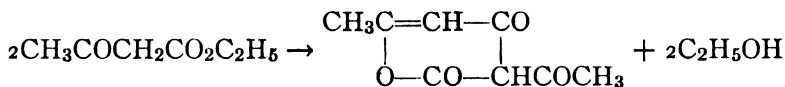
By the same procedure the following dibromides have been prepared.

	PER CENT YIELD	BOILING POINT
Trimethylene bromide.....	75	165–167°
Hexamethylene bromide.....	90	108–112°/8 mm.
Nonamethylene bromide.....	93	128–130°/2 mm.

### 3. Methods of Preparation

Decamethylene bromide was first prepared by heating the glycol in a sealed tube with fuming hydrobromic acid.<sup>1</sup> Later it was prepared in the manner here described.<sup>2,3</sup>

#### DEHYDROACETIC ACID



Submitted by F. ARNDT.

Checked by W. W. HARTMAN and A. WEISSBERGER.

#### 1. Procedure

A 250-cc. round-bottomed flask is fitted with a thermometer reaching nearly to the bottom (Note 1) and a 3- or 4-bulb fractionating column without a side arm, at the upper end of which is attached a partial condenser (Fig. 3) (Note 2). The side arm (A) of the latter carries a 110° thermometer and is connected to a condenser set for downward distillation. The inside container (B) of the partial condenser is filled halfway with toluene, a chip of porous plate is added, and the top is attached to a reflux condenser.

In the 250-cc. flask 100 g. (0.78 mole) of freshly vacuum-distilled ethyl acetoacetate and 0.05 g. of sodium bicarbonate (Note 3) are placed and heated so that the toluene is just kept boiling until the liquid in the flask has reached 200–210° (Note 4). The time for heating is usually seven to eight hours, during which period 27 g. of distillate boiling at 72° (mostly alcohol) is collected, and the color of the reaction mixture becomes dark brown. The dehydroacetic acid, while still hot (Note 5), is transferred to a 200-cc. distilling flask (Note 6) and distilled *in vacuo*. After a

<sup>1</sup> Franke and Hankam, *Monatsh.* **31**, 181 (1910).

<sup>2</sup> Chuit, *Helv. Chim. Acta* **9**, 264 (1926).

<sup>3</sup> Carothers, Hill, Kirby, and Jacobson, *J. Am. Chem. Soc.* **52**, 5279 (1930).

fore-run boiling up to  $128^{\circ}$  at 12 mm., consisting of ethyl acetoacetate, has been collected, the receiver is changed and dehydroacetic acid is collected up to  $140^{\circ}$  at 12 mm. The yield of dehy-

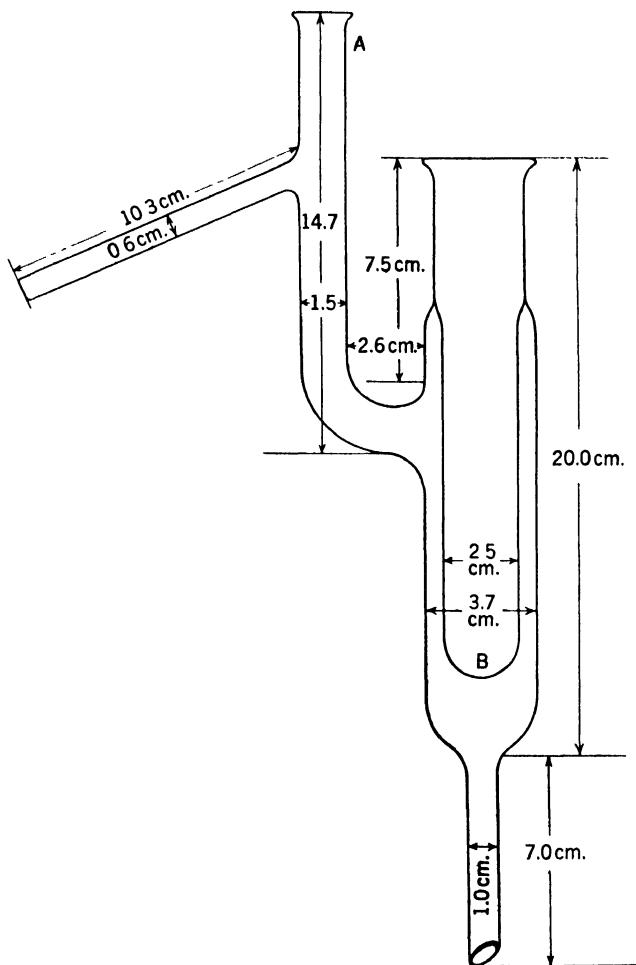


FIG. 3.

droacetic acid melting at  $104-110^{\circ}$  is 34 g. (53 per cent of the theoretical amount) (Note 7). A purer product, m. p.  $108^{\circ}$ , may be secured in 80 per cent yield by recrystallization from ethyl alcohol, using 2 cc. per gram of material. (Note 8).

## 2. Notes

1. The bulb of the thermometer must be immersed in the liquid.

2. This partial condenser, which is a modification of one described by Hahn,<sup>1</sup> is very effective in reducing the time required for fractional distillation of many mixtures. It is best constructed of Pyrex. The dimensions given are approximate and may be varied to suit individual needs. The inside container is a 30 by 140 mm. Pyrex test tube sealed at the top to standard Pyrex tubing. It is very effective in the purification of cyclohexene (Org. Syn. Coll. Vol. 1, 177).<sup>2</sup> The crude hydrocarbon mixture is first put into the flask with ethyl alcohol in the partial condenser, and the whole heated as long as a distillate is obtained. The alcohol is then replaced by ethylene chloride and the cyclohexene collected.

3. It is essential to use sodium bicarbonate to secure consistent results.

4. Above this temperature extensive decomposition sets in. The time required varies with the size of the run, being less with smaller quantities.

5. The residue solidifies on cooling. The dehydroacetic acid may be filtered and washed at this stage, but the yield is lower, owing to its solubility in the reaction mixture.

6. An ordinary 200-cc. distilling flask with a large-diameter side arm placed well down on the neck gave the best results. There was no foaming, frothing, or spattering.

7. The yield falls off with larger amounts; e.g., 500 g. of ester gave only 35 per cent of the calculated quantity of acid.

8. The acid may be isolated through the sodium salt, but the quality is poorer and the yield less.

## 3. Methods of Preparation

Dehydroacetic acid has been prepared by the action of acetic

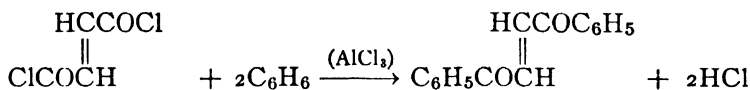
<sup>1</sup> Hahn, Ber. **43**, 419 (1910).

<sup>2</sup> A. W. Hutchison, private communication.



anhydride on acetonedicarboxylic acid,<sup>3</sup> as a by-product in the pyrolysis of acetone to give ketene,<sup>4</sup> by treatment of ketene dimer with pyridine,<sup>5</sup> and by removal of alcohol from acetoacetic ester.<sup>6</sup> The usual method of purification has been through the sodium salt.

**trans-DIBENZOYLETHYLENE**  
(2-Butene-1,4-dione, 1,4-Diphenyl-)



Submitted by R. E. LUTZ.

Checked by C. F. H. ALLEN and F. P. FINGERT.

### 1. Procedure

EIGHTEEN HUNDRED cubic centimeters of benzene (Note 1) and 350 g. of finely ground, anhydrous aluminum chloride (2.6 moles) (Note 2) are placed in a 3-l. three-necked flask, fitted with a mechanical stirrer, a dropping funnel (Note 3) containing 153 g. (1 mole) of fumaryl chloride (p. 51), and a reflux condenser (Note 4). A trap for absorbing hydrogen chloride (Org. Syn. 14, 2) is attached to the condenser.

The mixture is well stirred and heated externally by hot water (50–60°) (Note 5), the water removed, and the fumaryl chloride admitted at a *brisk* rate, moderated only enough to avoid a too rapid evolution of hydrogen chloride; this requires fifteen to twenty-five minutes (Notes 6 and 7). The mixture turns dark red and soon reaches the boiling point; hydrogen chloride is rapidly given off. The mixture is then refluxed gently for ten minutes with stirring.

The pasty red mixture is then poured portionwise upon 4 kg.

<sup>3</sup> von Pechmann, Ber. **24**, 3600 (1891); von Pechmann and Neger, Ann. **273**, 194 (1893).

<sup>4</sup> Hurd, Sweet, and Thomas, J. Am. Chem. Soc. **55**, 336 (1933).

<sup>5</sup> Chick and Wilshire, J. Chem. Soc. **93**, 946 (1908); **97**, 1987 (1910).

<sup>6</sup> Arndt and Nachtwey, Ber. **57**, 1489 (1924); Arndt, Eistert, Scholz, and Aron, ibid. **69**, 2373 (1936).

of cracked ice to which has been added 75 cc. of concentrated hydrochloric acid, the reaction mixture being thoroughly stirred before each pouring so that the aluminum chloride complex does not settle out and become concentrated at the bottom of the flask. The residue in the flask is decomposed by adding some of the ice and water. After standing twenty to thirty minutes, very hot water (Note 8) is added to melt any ice or frozen benzene and raise the temperature generally. The bulk of the aqueous layer is discarded by drawing it off with a glass tube which is connected to a suction flask. The benzene layer is next washed at least four times with hot water (Notes 8 and 9). Finally the warm benzene layer is transferred to a large separatory funnel, any crusts of dibenzoyl ethylene adhering to the various pieces of apparatus are dissolved in hot benzene, and the solutions combined; the small water layer is separated and discarded (Note 10). The hot benzene layer is then filtered, either by gravity using a large glass funnel or by suction on a Büchner funnel, into a 3-l. round-bottomed flask. After a few porcelain chips have been added, the bulk of the solvent is distilled, using a steam or boiling water bath. Most of the residual solvent is removed under diminished pressure, using a water pump, and heating until the syrupy liquid begins to crystallize suddenly (Note 11). At this point, the heating and suction are discontinued and 125 cc. of 95 per cent ethyl alcohol is added rapidly, stirring with a wooden paddle to break up any lumps. The flask is cooled a few minutes under the tap and the bright yellow product collected on a 127-mm. Büchner funnel. The solid is triturated on the funnel with cold alcohol for ten minutes to remove adhering mother liquor, and sucked as dry as possible. The yield is 186-197 g. (78-83 per cent of the theoretical amount) (Note 11), and the melting point is 109-110° (Notes 12 and 13).

## 2. Notes

1. The checkers used thiophene-free benzene, m. p. 5°; it gave a product of better quality than the commercial hydrocarbon. A large excess is used to facilitate stirring.

2. Resublimed aluminum chloride is suitable; it requires no further grinding. The excess over the required 2 moles assures a complete reaction and a product of good color.

3. A dropping funnel is preferred to the ordinary separatory funnel, since the rate of addition of the fumaryl chloride is important.

4. A wide-bore condenser permits a more rapid reaction, favoring an increased yield and better product.

5. If the mixture is not heated before the fumaryl chloride is added the reaction is slow, and when the temperature finally rises the accumulated chloride and intermediates react so vigorously that frothing and boiling over occur.

6. If for any reason stirring is interrupted, the *addition* of fumaryl chloride *must be stopped immediately*, and the stirrer started again *very cautiously*.

7. The product and yield are better with the shorter time of addition.

8. Very hot water is desirable; unless the benzene layer is really warm ( $50-60^{\circ}$ ), the separation into layers is poor and the product does not readily dissolve. For the same reasons, hot water is used in the subsequent washings.

9. The first and second wash waters should be acidulated with 25 cc. of concentrated hydrochloric acid; this facilitates the formation of layers.

10. If the water used has been hot enough to keep the benzene really warm ( $50-60^{\circ}$ ), there are no crusty deposits.

11. Ordinarily there is but 8 g. in the second crop; however, in the event that not enough solvent has been removed, there may be a larger amount, with a correspondingly smaller first crop. The total yield is 194-205 g. (82-86 per cent of the theoretical amount). If the first crop weighs over 190 g., it is not economical to work up the mother liquor.

12. In some runs, the product sinters slightly at  $106^{\circ}$ , but the melting point is unaltered.

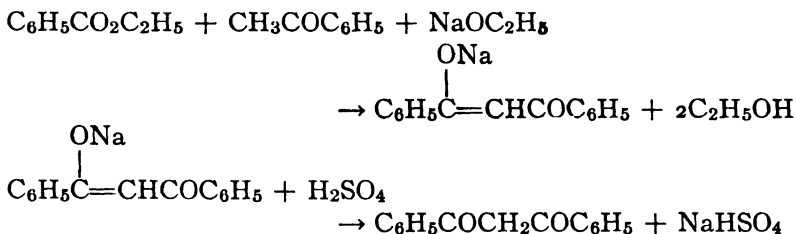
13. Lower-melting material, whatever its source, can be recrystallized from 95 per cent alcohol, using 3 cc. per gram.

### 3. Methods of Preparation

*trans*-Dibenzoylethylene has been prepared by the present method,<sup>1</sup> by heating dibenzoylmalic acid,<sup>2</sup> by condensing benzoylformaldehyde and acetophenone,<sup>3</sup> and by the Friedel-Crafts reaction on benzoylacrylyl chloride.<sup>4</sup> Analogs may be prepared using other aromatics such as mesitylene,<sup>1,4,5,9</sup> with carbon disulfide as the solvent, and also using other acid chlorides such as mesaconyl chloride,<sup>6</sup> dibromofumaryl chloride,<sup>7</sup> and dimethylfumaryl chloride.<sup>8</sup>

#### DIBENZOYLMETHANE

##### (1,3-Propanedione, 1,3-Diphenyl-)



Submitted by ARTHUR MAGNANI and S. M. McELVAIN.

Checked by R. L. SHRINER and F. J. WOLF.

#### 1. Procedure

IN a dry 2-l. three-necked flask are placed 600 g. (4 moles) of freshly distilled ethyl benzoate and 60 g. (0.5 mole) of freshly distilled acetophenone (Note 1). The flask is fitted with a mer-

<sup>1</sup> Conant and Lutz, J. Am. Chem. Soc. **45**, 1305 (1923); Oddy, *ibid.* **45**, 2159 (1923).

<sup>2</sup> Paal and Schulze, Ber. **33**, 3798 (1900).

<sup>3</sup> Smedley, J. Chem. Soc. **95**, 219 (1909).

<sup>4</sup> Lutz, J. Am. Chem. Soc. **52**, 3432 (1930).

<sup>5</sup> Conant and Lutz, *ibid.* **47**, 891 (1925).

<sup>6</sup> Lutz and Taylor, *ibid.* **55**, 1177 (1933).

<sup>7</sup> Lutz, *ibid.* **52**, 3421 (1930).

<sup>8</sup> Lutz and Taylor, *ibid.* **55**, 1599 (1933).

<sup>9</sup> Weygand and Lanzendorf, J. prakt. Chem. **151**, 209 (1938).

cury-sealed stirrer which must be rugged enough to stir the reaction mixture even after it becomes very viscous (Note 2). A condenser for downward distillation is attached to one of the necks, and a 500-cc. filter flask is used as the receiver. This receiver is connected to a water pump through a suction flask carrying a two-holed rubber stopper, one hole of which is left open. The reaction flask is heated in an oil bath kept at 150–160°, and, after the mixture is hot, 44 g. (0.65 mole) of sodium ethoxide (Note 3) is added through the third arm of the flask in 1- to 2-g. portions. The ethoxide addition can be conveniently accomplished with a spoon shaped to enter the arm of the flask or by placing a very short-stemmed large funnel in the third neck and pushing the ethoxide through the funnel with a small glass rod or wire spatula. The reaction mixture becomes orange immediately; alcohol distils after the first few additions, and thereafter the evolution of alcohol is quite vigorous. The additions are made as rapidly as evolution of the alcohol permits. During the ethoxide addition a gentle stream of air is kept passing through the flask by means of a water pump attached to the receiver in order to prevent the alcohol vapor from rising in the third arm of the flask and interfering with the addition (Note 4).

After all the ethoxide has been added (twenty to thirty minutes) the gelatinous reaction mixture is stirred until no more distillate comes over (fifteen to thirty minutes). The weight of this distillate amounts to 38–45 g. (Note 5).

The oil bath is removed, and, with the stirring maintained, the reaction mixture is cooled to room temperature by running cold water over the flask. Then 150 cc. of water is added to dissolve the reaction mass, and both layers of the mixture are transferred to a separatory funnel. An ice-cold solution of 25 cc. of concentrated sulfuric acid in 200 cc. of water is added, and the mixture is shaken vigorously. The ester layer is separated and washed with 200 cc. of water; it is then shaken with successive 200-cc. portions of 5 per cent sodium bicarbonate solution until the evolution of carbon dioxide ceases, after which it is washed with 200 cc. of water. The bicarbonate solution is separated and extracted with 100 cc. of ether (Note 6). The ether extract,

after washing with 50 cc. of water, is combined with the ester layer and the resulting ethereal solution dried with 40 g. of calcium chloride. The ether is removed by distillation from a water bath, and the excess ethyl benzoate is removed by distillation under reduced pressure. The recovered ester, b.p.  $80-83^{\circ}/8$  mm., amounts to 475-490 g. After the ester is removed the temperature of the oil bath is slowly raised to  $180-185^{\circ}$  while the system is maintained under 8 mm. pressure. A small amount of liquid distilling higher than the ester is thus removed. When no more distillate comes over at this temperature, the remaining oil, while still warm, is poured into a 500-cc. Erlenmeyer flask and allowed to crystallize. This crude dibenzoylmethane weighs 92-108 g. and is usually brown in color. It is recrystallized by dissolving in 150 cc. of hot methyl alcohol, adding 1 g. of Norite, filtering, and cooling the filtrate to  $0^{\circ}$  (Note 7). The yield of yellow crystals of dibenzoylmethane, m.p.  $77-78^{\circ}$  (Note 8), thus obtained is 70-80 g. (62-71 per cent of the theoretical amount based on the acetophenone).

## 2. Notes

1. The apparatus and all reagents must be carefully dried.
2. A thick glass rod stirrer bent to fit around the inside of the flask works well. The mixture is too viscous to be stirred with a Hershberg stirrer.
3. The sodium ethoxide should be freshly prepared according to the directions under acetylacetone (p. 8). It must be kept in a tightly stoppered bottle and handled quickly.
4. The water flow through the pump is so regulated that no appreciable vacuum is allowed to build up in the reaction flask when the side arm through which the ethoxide is added is closed.
5. The amount of this distillate depends somewhat upon the rate of flow of air through the apparatus. If an appreciable vacuum builds up, this distillate may contain some acetophenone.
6. By acidification of the aqueous bicarbonate layer, 20 to 25 g. of benzoic acid may be obtained.
7. If the product is still dark colored, it may be purified by

recrystallization from 400 cc. of 90 per cent methyl alcohol and the color removed with Norite. In either method of crystallization 4 to 6 g. of inferior product may be obtained from the mother liquor.

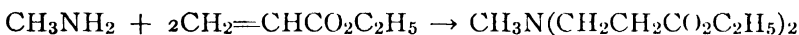
8. Occasionally crystals melting at 71–72° may be obtained which upon standing change to the higher-melting form.

### 3. Methods of Preparation

In addition to the methods listed in Org. Syn. Coll. Vol. 1, 200, may be added the formation of dibenzoylmethane when certain alkyl benzoates are treated with sodium ethoxide.<sup>1</sup>

## DI- $\beta$ -CARBETHOXYETHYLMETHYLAMINE

(Propionic Acid,  $\beta,\beta'$ -Methylimino-bis-, Diethyl Ester)



Submitted by RALPH MOZINGO and J. H. MCCracken.

Checked by C. F. H. ALLEN and JOSEPH DEC.

### 1. Procedure

IN a 2-l. flask, fitted with a rubber stopper carrying a soda-lime drying tube and a glass tube reaching almost to the bottom, is placed 325 g. (420 cc.) of absolute ethyl alcohol. The whole is then tared, placed in an ice bath, and the inlet tube is connected to a source of dry methylamine.

The methylamine generator consists of a 1-l. flask fitted with a dropping funnel and outlet tube, which in turn is connected to a 25-cm. drying tower containing soda-lime, followed by a 1-l. safety trap (Note 1). In the flask is placed 200 g. of technical sodium hydroxide flakes, and 263 g. of a 33–35 per cent solution of methylamine in water (Note 2) is dropped in slowly at such a rate that an even current of gas is evolved. When the addition has been completed and the gas bubbles very slowly into the

<sup>1</sup> Magnani and McElvain, J. Am. Chem. Soc. 60, 813 (1938).

alcohol, the flask and contents are removed and weighed; the increase should be 84–86 g. (2.71–2.77 moles) (Note 3).

The flask is reimmersed in the ice bath, and 900–925 g. (5.4–5.5 moles), depending upon the weight of methylamine, of a 60 per cent solution of ethyl acrylate in ethyl alcohol (Note 4) is added in portions of about 100 cc. at such a rate that the temperature of the mixture does not rise above 40°; this requires about ten minutes. After each addition the flask is stoppered to exclude moisture. When all the ester has been added the flask is closed by a rubber stopper and allowed to stand six days (Note 5).

Most of the alcohol is removed by distillation (one and one-half hours) on a steam bath and the residue transferred to a modified Claisen flask and distilled. The fraction boiling below 50° at 20 mm. (Note 6) is removed with the aid of a water pump and the residue distilled using an oil pump (at 3 mm. pressure) (Note 7). The portion boiling at 105–108° at 3 mm. (Note 8) is collected as di- $\beta$ -carbethoxyethylmethylamine (Note 9); it amounts to 519–550 g. (83–86 per cent of the theoretical amount) (Note 10).

## 2. Notes

1. The safety trap is important, since the alcohol tends to suck back easily.

2. Solutions of methylamine in water are obtainable from Eastman Kodak Company (33 per cent) and Röhm and Haas Company (35 per cent).

3. It is much more convenient to use the amount of methylamine secured than to try to collect a predetermined weight.

4. The ethyl acrylate (60 per cent solution in alcohol) is available from the Röhm and Haas Company. The solution, containing a polymerization inhibitor, is used without treatment. The inhibitor must not be removed.

5. If the time is shortened, the yield is correspondingly decreased.

6. Most of this distillate comes over with the oil-bath temperature at 75°; the temperature is finally raised to 150°. The



fractionating arm of the Claisen flask used was wrapped with asbestos cord.

7. Any ethyl *N*-methyl- $\beta$ -aminopropionate formed comes over in the first or middle fraction (6–8 cc.). The middle fraction is obtained as the fraction boiling up to  $105^\circ$  at 3 mm., on changing from the water pump to an oil pump. The oil bath is cooled to  $100^\circ$  before applying the higher vacuum.

8. The observed boiling points vary with the particular apparatus used.

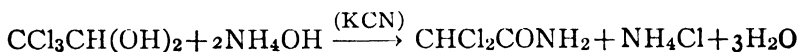
9. Since the ester decomposes very slightly during distillation, the oil pump should be protected from ethyl acrylate and methylamine by a Dry Ice trap. The distillation should not be interrupted.

10. Di- $\beta$ -carbomethoxyethylmethylamine may be prepared in a similar yield by substituting an equivalent quantity of methyl acrylate in methyl alcohol in the above procedure.

### 3. Methods of Preparation

This ester has been prepared by the action of ethyl  $\beta$ -bromopropionate on methylamine hydrochloride in the presence of silver oxide,<sup>1</sup> by the addition of methylamine to ethyl acrylate,<sup>2</sup> and by heating ethyl  $\beta$ -chloropropionate, methylamine, and benzene in an autoclave.<sup>3</sup>

### $\alpha,\alpha$ -DICHLOROACETAMIDE



Submitted by JOHN R. CLARK, W. J. SHIBE, and RALPH CONNOR.

Checked by R. L. SHRINER and NEIL S. MOON.

#### 1. Procedure

A SOLUTION of 134 g. (0.81 mole) of chloral hydrate (Note 1) in 400 cc. of ether (Note 2) is placed in a 2-l. round-bottomed,

<sup>1</sup> McElvain, J. Am. Chem. Soc. **46**, 1724 (1924).

<sup>2</sup> Morsch, Monatsh. **63**, 229 (1933).

<sup>3</sup> Ger. pat. 491,877 [Frdl. **16**, 2908 (1931)] [C. A. **24**, 2468 (1930)].

three-necked flask equipped with a dropping funnel, a reflux condenser, and an efficient mercury-sealed stirrer (Note 3). A solution of 12 g. of potassium cyanide (Note 4) in 220 cc. of concentrated ammonium hydroxide (sp. gr. 0.9) is added through the dropping funnel over the course of fifteen minutes at a rate sufficient to cause the ether to reflux vigorously. Stirring is continued for an additional twenty minutes (Note 5). The layers are separated and the ether layer washed once with 75 cc. of water and once with 75 cc. of 10 per cent aqueous sulfuric acid solution (Note 6). (These washings are retained and used again later.) The aqueous layer from the reaction mixture is extracted with three 75-cc. portions of ether, and each ether extract is washed successively with the same water and sulfuric acid solutions used previously. The combined ether extracts are dried with 40 g. of sodium sulfate, the ether removed by distillation, and the residue recrystallized from 200 cc. of benzene. The solid is removed by filtration with suction and washed with two 25-cc. portions of cold benzene. The yield is 66.76 g. melting at 97.5–99.5° (corr.). Concentration of the filtrate gives 1–5 g. of material with a slightly lower (96–97° corr.) melting point, making the total yield 67.81 g. (65.78 per cent of the theoretical amount).

## 2. Notes

1. The chloral hydrate was of U.S.P. XI quality.
2. Ether decreases the amount of charring, presumably by controlling the temperature of the reaction mixture.
3. It is very difficult to prevent the escape of ammonia and ether. The reaction should be carried out in a hood.
4. Baker's potassium cyanide, 94–96 per cent, was used.
5. A decided increase in reaction time will cause charring and give a product that is difficult to purify. The reaction should not be interrupted until the ethereal extracts have been washed as described.
6. The ethereal extracts of the reaction mixture contain impurities which cause charring when the solvent is removed. The water and acid treatments remove these impurities. Equally

good yields may be obtained by omitting these washings, but then it is necessary to decolorize with Norite in the recrystallization from benzene and a second recrystallization may be necessary to obtain a white product.

### 3. Methods of Preparation

Dichloroacetamide has been prepared from ethyl dichloroacetate with alcoholic ammonia<sup>1</sup> or aqueous ammonium hydroxide,<sup>2</sup> from ethyl dichloromalonate and alcoholic ammonia,<sup>3</sup> by the action of ammonia on pentachloroacetone,<sup>4</sup> chloral cyanohydrin,<sup>5</sup> and hexachloro-1,3,5-cyclohexanetrione,<sup>6</sup> from chloral ammonia and potassium cyanide,<sup>7</sup> by the action of hydrogen chloride on dichloroacetonitrile,<sup>8</sup> from the reaction of asparagine with the sodium salt of *N*-chloro-*p*-toluenesulfonamide,<sup>9</sup> and by the action of an alkali cyanide and ammonia on chloral hydrate.<sup>10</sup>

<sup>1</sup> Geuther, Jahresbericht der Chemie (1864), 317.

<sup>2</sup> d'Ouville and Connor, J. Am. Chem. Soc. **60**, 33 (1938).

<sup>3</sup> Conrad and Bruckner, Ber. **24**, 2993 (1891); Dootson, J. Chem. Soc. **75**, 169 (1899).

<sup>4</sup> Cloez, Compt. rend. **53**, 1122 (1864).

<sup>5</sup> Pinner and Fuchs, Ber. **10**, 1058 (1877).

<sup>6</sup> Zincke and Kegel, ibid. **23**, 230 (1890).

<sup>7</sup> Schiff and Speciale, Gazz. chim. ital. **9**, 335 (1879).

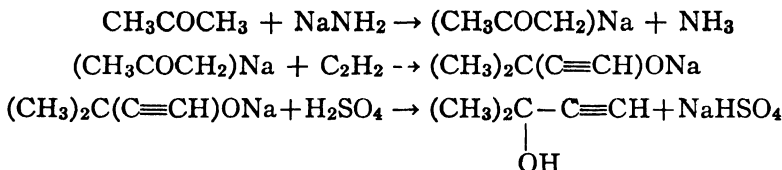
<sup>8</sup> Steinkopf and Malinowski, Ber. **44**, 2898 (1911).

<sup>9</sup> Dakin, Biochem. J. **11**, 79 (1917).

<sup>10</sup> Chattaway and Irving, J. Chem. Soc. (1929), 1038.

## DIMETHYLETHYNYL CARBINOL

(3-Butyn-2-ol, 2-Methyl-)



Submitted by DONALD D. COFFMAN.

Checked by C. F. H. ALLEN and ALAN BELL.

### 1. Procedure

IN a 2-l. round-bottomed flask fitted with a three-holed stopper bearing a mechanical stirrer, separatory funnel, and a gas outlet tube leading to a hood (Note 1) are placed 1000 cc. of anhydrous ether (Note 2) and 156 g. (4 moles) of finely ground sodium amide (p. 86) (Note 3). The flask is surrounded by a well-packed ice-salt bath. To the vigorously stirred mixture 232 g. (4 moles) of dry acetone (Note 4) is added, dropwise, during a period of three hours. With the flask cooled to  $-10^\circ$  (Note 5), a slow current of acetylene (Note 6) is passed through the reaction mixture for two hours to sweep out the ammonia. The three-holed stopper is then replaced by a two-holed stopper having a stopcock and an inlet tube reaching to the bottom of the flask and connected with a cylinder of acetylene. The stopper is wired in. The mixture is placed in an ice-salt mixture (Note 5), the whole being mounted on a shaking machine and agitated vigorously for ten hours; the mixture is kept under a pressure of 10 lb. of acetylene. Every half hour the pressure is released by means of the stopcock, to sweep out ammonia formed from small amounts of previously unreacted sodium amide.

The reaction mixture is poured cautiously into 800 g. of crushed ice and acidified in the cold by the addition of 400 cc. of 10 *N* sulfuric acid (Note 7). The ether layer is separated and the aqueous layer extracted twice with 100-cc. portions of ether.

The combined ethereal solutions are dried over 100 g. of anhydrous potassium carbonate, and the filtered solution is fractionated (Note 8). The portion boiling at 103–107° is collected; any low-boiling fraction is dried and redistilled. The total yield is 135–155 g. (40–46 per cent of the theoretical amount) of a colorless product that boils at 103–107° (Notes 9, 10 and 11).

## 2. Notes

1. In cold weather, it is convenient to carry out the reaction out-of-doors. This minimizes the attention needed to replace the ice. The outlet tube then opens to the air.

2. A commercial grade of anhydrous ether was dried over sodium.

3. The sodium amide, moistened by the heptane, was rapidly ground and the solvent allowed to evaporate.

4. An Eastman grade of acetone was used, after standing over anhydrous potassium carbonate.

5. It was found convenient to add Dry Ice to the freezing mixture, thus decreasing the frequency of packing. The temperature never rose above  $-10^{\circ}$  and was usually considerably less.

6. Commercial acetylene used for welding was dried by passing over anhydrous calcium chloride.

7. This is prepared by adding 110 cc. of concentrated sulfuric acid to 290 cc. of water.

8. The checkers used a modified Widmer column (p. 53).

9. There is a considerable quantity of high-boiling material; the quantity and boiling-point range are greater when the shaking is insufficient.

10. The reaction may be interrupted at several points. After the ammonia has been swept out by acetylene, it is usually convenient to place the mixture in a refrigerator overnight and start the shaking the next day. The shaking period need not be continuous; in this event the chilled mixture is placed in the icebox.

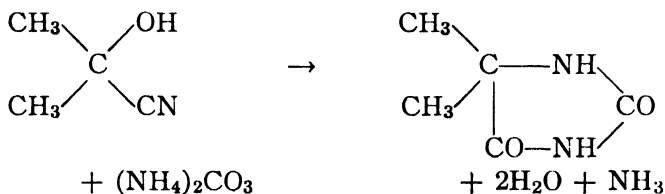
11. By the same procedure the submitter obtained methylethyne-1-yn-1-yl carbinol, b.p. 119–123° (33 per cent yield),

using methyl ethyl ketone,<sup>1,2</sup> and 1-ethynyl cyclohexanol-1, b.p. 53-55°/2 mm. (50 per cent yield), using cyclohexanone and double the amount of ether.

### 3. Methods of Preparation

Dimethylethynyl carbinol has usually been prepared by the addition of acetylene to the sodium derivative of acetone,<sup>3,4,5,6,7,8</sup> but potassium metal<sup>9</sup> and sodium ethoxide<sup>10</sup> have also been used. The above method is based upon that described by Sung Wou-seng.<sup>3</sup> A more recent method uses potassium hydroxide, calcium carbide, and acetone.<sup>11</sup>

#### 5,5-DIMETHYLHYDANTOIN



Submitted by E. C. WAGNER and MANUEL BAIZER.

Checked by C. F. H. ALLEN and G. F. FRAMM.

### 1. Procedure

IN a 600-cc. beaker are mixed 85 g. (1 mole) of acetone cyanohydrin (Note 1) and 150 g. (1.31 moles) of freshly powdered ammonium carbonate. The mixture is warmed on a steam bath, preferably in a hood (Note 2), and stirred with a thermometer

<sup>1</sup> Ger. pat. 289,800 [Frld. 12, 57 (1914-6)].

<sup>2</sup> Ger. pat. 285,770 [Frld. 12, 55 (1914-6)].

<sup>3</sup> Sung Wouseng, Ann. chim. (10) 1, 359 (1924).

<sup>4</sup> Scheibler and Fischer, Ber. 55, 2903 (1922).

<sup>5</sup> Ger. pat. 280,226 [Frld. 12, 51, (1914-6)].

<sup>6</sup> U. S. pat. 2,106,180 [C. A. 32, 2547 (1938)].

<sup>7</sup> Ger. pat. 286,920 [Frld. 12, 54, (1914-6)].

<sup>8</sup> Froning and Hennion, J. Am. Chem. Soc. 62, 654 (1940).

<sup>9</sup> Ger. pat. 284,764 [Frld. 12, 53 (1914-6)].

<sup>10</sup> Ger. pat. 291,185 [Frld. 12, 56, (1914-6)].

(Note 3). Gentle action begins around  $50^{\circ}$  and continues during about three hours at  $68-80^{\circ}$ . To complete the reaction and to decompose excess ammonium carbonate, the temperature is finally raised to  $90^{\circ}$  and maintained at this point until the liquid mixture is quiescent (thirty minutes). The residue is colorless or pale yellow (Note 1) and solidifies on cooling. It is dissolved in 100 cc. of hot water, digested with Norite, and filtered rapidly through a heated filter. The filtrate is evaporated on a hot plate until crystals appear at the surface of the liquid, which is then chilled in an ice bath. The white crystals are filtered with suction; the filter cake is pressed and sucked dry and then washed twice with small portions (5-7 cc.) of ether, each portion being well incorporated with the crystals and then drawn through with suction. The mother liquor is concentrated as before to a volume of 25 cc. or less and chilled, and a further crop of crystals is obtained by repetition of the operations outlined (Note 4). The yield is 65-72 g. (51-56 per cent of the theoretical amount). The first crop is nearly pure and melts at  $173^{\circ}$ ; the second crop melts at about  $164^{\circ}$ .

The dimethylhydantoin is dissolved in the least boiling water (about 65 cc.) and digested with charcoal, and the hot solution is filtered through a heated filter. The filtrate is chilled, and the separated crystals are filtered with suction and washed sparingly with cold water. The recovery is about 80-85 per cent of the crude weight. The recrystallized product melts at  $174-175^{\circ}$  ( $178^{\circ}$  corr.). A further crop of less pure material (m.p.  $171-172^{\circ}$ ) may be obtained by concentration of the mother liquor to small volume (Note 5).

## 2. Notes

1. Acetone cyanohydrin (Org. Syn. 15, 1) is entirely satisfactory. For immediate use, a less pure cyanohydrin will serve; this is readily made as follows.<sup>1</sup>

A solution of 165 g. (pure basis) of sodium bisulfite in 300 cc. of cold water is transferred to a 1-l. flask, which is cooled in an

<sup>1</sup> Houben, "Die Methoden der organischen Chemie," 3rd Ed., Vol. III, p 568, Verlag Georg Thieme, Leipzig, 1930.

ice bath, while 87 g. of acetone is dropped in slowly with rotation of the flask. A solution of 100 g. (pure basis) of potassium or 75 g. of sodium cyanide in 300 cc. of cold water is then added gradually. The cyanohydrin separates as an upper layer; when sodium cyanide is used, this separation is slower and is not complete until the mixture has come to room temperature. It is drawn off and dried for several hours over sodium sulfate in a stoppered flask kept in the dark. The yield is about 90 g. (70 per cent of the theoretical amount); it may be somewhat increased by ether extraction of the aqueous liquid.

Acetone cyanohydrin so prepared is colorless, or nearly so, and if used promptly is satisfactory for the preparation of dimethylhydantoin. If it is kept more than a day or two, the cyanohydrin may become deep red and will then impart a red color to the dimethylhydantoin which is difficult to remove.

2. The reaction mixture evolves ammonia slowly in amounts which are unpleasant though tolerable in a well-ventilated room.

3. During most of the reaction, the mixture is partly solid or very viscous and cannot be stirred properly by a mechanically operated stirrer of the usual type. The Hershberg stirrer (Org. Syn. 17, 31) is unsatisfactory.

4. Dimethylhydantoin is highly soluble in hot water, and its solubility in cold water is considerable. Several crops may be removed by successive concentrations of the mother liquors, taken finally to very small volume. The conversion of acetone cyanohydrin to dimethylhydantoin is said to be practically quantitative.<sup>2</sup>

5. The method described serves for the preparation of various 5-substituted or 5,5-disubstituted hydantoins, using appropriate cyanohydrins. With methylethylketone cyanohydrin there was obtained a 75 per cent yield of 5-methyl-5-ethylhydantoin, m.p. 141.5°.

### 3. Methods of Preparation

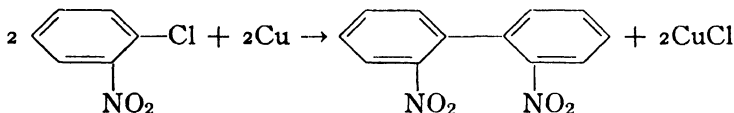
Hydantoins with one or two substituents in the 5-position have been prepared by heating cyanohydrins with urea and treating

<sup>2</sup> Bucherer and Steiner, J. prakt. Chem. 140, 291 (1934).



this reaction mixture with moderately concentrated hydrochloric acid;<sup>3</sup> by heating alanine sulfate with potassium cyanate;<sup>4</sup> by the action of phosgene or oxalyl chloride<sup>5</sup> or carbonic esters<sup>6</sup> on *C*-substituted aminoacetamides; by the fusion of amino acids with urea;<sup>7</sup> by the action of potassium cyanate on  $\alpha$ -aminonitrile hydrochlorides, and heating the resulting ureido-nitriles with dilute hydrochloric acid;<sup>8</sup> by heating aldehydes or ketones with alkali cyanide and ammonium carbonate under pressure of several atmospheres of carbon dioxide;<sup>9</sup> by warming cyanohydrins with ammonium carbonate;<sup>2</sup> by the interaction of ketone or aldehyde and ammonium carbonate with hydrogen cyanide or alkali cyanide, in ligroin or in 50 per cent alcohol, at room temperature or at 50–80°;<sup>10</sup> or by the interaction of ketone or aldehyde bisulfite compounds with cyanide and ammonium carbonate.<sup>10</sup> The procedure described<sup>11</sup> is that of Bucherer and Steiner.<sup>2</sup>

### 2,2'-DINITROBIPHENYL



Submitted by REYNOLD C. FUSON and E. A. CLEVELAND.

Checked by W. E. BACHMANN, A. L. WILDS, and J. KORMAN.

### 1. Procedure

IN a 1-l. flask equipped with a mechanical stirrer are placed 200 g. (1.27 moles) of *o*-chloronitrobenzene and 300 g. of clean

<sup>3</sup> Pinner, Ber. **20**, 2355 (1887); **21**, 2320 (1888).

<sup>4</sup> Urech, Ann. **165**, 99 (1873).

<sup>5</sup> Ger. pat. 310,427 [Frdl. **13**, 803 (1923–4)].

<sup>6</sup> Read, J. Am. Chem. Soc. **44**, 1749 (1922).

<sup>7</sup> Griess, Ber. **2**, 47 (1869); Halpern, Monatsh. **17**, 243 (1896).

<sup>8</sup> Herbst and Johnson, J. Am. Chem. Soc. **54**, 2465 (1932).

<sup>9</sup> Bergs, Ger. pat. 566,094 (1929) [C. A. **27**, 1001 (1933)].

<sup>10</sup> Bucherer and Lieb, J. prakt. Chem. **141**, 5 (1934).

<sup>11</sup> Wagner and Simons, J. Chem. Education **13**, 266 (1936).

dry sand. The mixture is heated in an oil bath to  $215-225^{\circ}$ , and then 200 g. of copper bronze (Note 1) is slowly added, the addition requiring about eighty minutes (Note 2). The temperature is kept at  $215-225^{\circ}$  for ninety minutes longer, the stirring being continued throughout. The mixture is poured while hot into a beaker containing 300-500 g. of sand and is then stirred until small clumps are formed; upon cooling, these are broken up in a mortar (Note 3). The mixture is boiled ten minutes with two 1.5-l. portions of alcohol and removed by filtration each time. The filtrates are cooled in an ice bath, and the 2,2'-dinitrobiphenyl is collected on a filter (Note 4). A second crop is obtained by concentrating the filtrate. The product is dissolved in hot alcohol (Note 5), and the solution is treated with Norite, filtered, and cooled in an ice bath. The solid is recrystallized from hot alcohol and is obtained as pure, yellow crystals melting at  $123.5-124.5^{\circ}$  (corr.). The yield is 80-95 g. (52-61 per cent of the theoretical amount).

## 2. Notes

1. Ordinary copper bronze does not always give satisfactory results in the Ullmann reaction. More uniform results are obtained if the copper bronze is prepared as suggested by Kleiderer and Adams.<sup>1</sup> The copper bronze is treated with 2 l. of a 2 per cent solution of iodine in acetone for five to ten minutes. The product is then collected on a Büchner funnel, removed, washed by stirring into a slurry with 1 l. of a 1:1 solution of concentrated hydrochloric acid in acetone, and again filtered. The copper iodide dissolves, and the copper bronze remaining is separated by filtration and washed with acetone. It is then dried in a vacuum desiccator. It should be used immediately.

2. The temperature of the mixture must not be allowed to rise much above  $240^{\circ}$  or reduction of the nitro groups will occur and carbazole will be formed.

3. The reaction mixture should not be allowed to cool in the flask, as it will set to a hard mass; it is almost impossible to remove this from the flask.

<sup>1</sup> Kleiderer and Adams, J. Am. Chem. Soc. **55**, 4225 (1933).

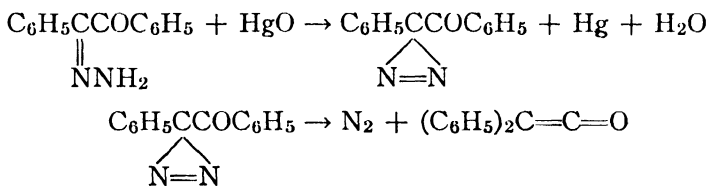
4. If the first two extractions with alcohol do not yield about 90 g. of crude product, a third extraction of the sand and residue is well worth while (the yield of impure product was never less than 90 g. when this procedure was carried out).

5. If the impure material is recrystallized from the minimum amount of alcohol, the suction funnel will become rapidly plugged during filtration with consequent loss of time and material. Two liters of alcohol per 100 g. of 2,2'-dinitrobiphenyl is preferable. All filtrates were reduced to a small volume, and the crude material obtained was recrystallized twice, using Norite. (This amounted to about 10 per cent of the total yield.)

### 3. Methods of Preparation

2,2'-Dinitrobiphenyl has been prepared by the action of copper on *o*-chloronitrobenzene or *o*-bromonitrobenzene,<sup>2</sup> and on diazotized *o*-nitroaniline.<sup>3</sup>

### DIPHENYLKETENE



Submitted by LEE IRVIN SMITH and H. H. HOEHN.

Checked by NATHAN L. DRAKE and JONATHAN WILLIAMS.

### 1. Procedure

FIFTY-SIX grams (0.25 mole) of benzil monohydrazone (Org. Syn. 15, 62) (Note 1) is mixed in a mortar with 81 g. (0.38 mole) of yellow mercuric oxide and 35 g. of anhydrous calcium sulfate (Note 2). The mixture is introduced into a 1-l. three-necked

<sup>2</sup> Ullmann and Bielecki, Ber. 34, 2174 (1901).

<sup>3</sup> Niementowski, ibid. 34, 3325 (1901).

flask fitted with a stirrer, a condenser, and a thermometer. The flask is placed in a water bath, 200 cc. of dry thiophene-free benzene is added, and the suspension is stirred at 25–35° (thermometer in solution) for four hours (Notes 3 and 4). The reaction mixture is filtered through a fine-grained filter paper, with slight suction, and the residue is washed with dry benzene until the washings are colorless.

The benzene solution of the diazo compound is poured into a separatory funnel protected with a drying tube and connected to a 125-cc. Claisen distilling flask provided with a condenser set for downward distillation and arranged so that it can be heated in a bath of Wood's metal. The temperature of the metal bath being maintained at 100–110°, the benzene solution is dropped slowly into the hot flask. Under these conditions, the benzene is removed by distillation, and the diazo compound transformed into diphenylketene. The residue is distilled *in vacuo* in an atmosphere of nitrogen, and the fraction boiling at 115–125° at 3–4 mm. (Note 5) is collected. The yield is 31 g. (64 per cent of the theoretical amount) of a product which, on redistillation, yields 28 g. of diphenylketene boiling at 119–121° at 3.5 mm. (58 per cent of the theoretical amount).

Diphenylketene is best stored in an atmosphere of nitrogen; the addition of a small crystal of hydroquinone serves to inhibit polymerization (Note 6).

## 2. Notes

1. Benzil monohydrazone can also be obtained in practically quantitative yield using hydrazine hydrate, a method first suggested by Curtius and Thun.<sup>1</sup> Hydrazine hydrate (45 g., 0.75 mole, of an 85 per cent solution of hydrazine hydrate in water) is slowly dropped into a hot solution of benzil (158 g., 0.75 mole) in alcohol (300 cc.) with stirring. The product begins to separate from the hot solution after three-fourths of the hydrazine hydrate has been added. The solution is heated under reflux for a period of five minutes after all the hydrazine hydrate has been added.

<sup>1</sup> Curtius and Thun, J. prakt. Chem. (2) 44, 176 (1891).

The flask is then cooled to  $0^{\circ}$ , and the hydrazone is filtered off and washed twice on the funnel with 100-cc. portions of cold alcohol. The product melts at  $149-151^{\circ}$  with decomposition.

2. Anhydrous calcium sulfate removes the water formed in the oxidation.

3. Considerable heat is generated at the beginning of the reaction, and ice must be used in the water bath to keep the temperature within the prescribed limits. After ten to fifteen minutes the ice is removed, and the temperature is maintained at  $25-35^{\circ}$  by the water bath.

4. Best results are obtained when the reaction mixture is stirred for four hours.

5. A viscous red residue always remains in the distilling flask, necessitating superheating to remove the last traces of diphenylketene.

6. According to the submitters, the preparation has been carried out using twice the quantities of material throughout with no loss in yield of diphenylketene.

### 3. Methods of Preparation

Diphenylketene has been prepared by action of tripropylamine on diphenylacetyl chloride,<sup>2</sup> by treating diphenylchloroacetyl chloride with granulated zinc,<sup>3</sup> and by the action of quinoline on diphenylacetyl chloride.<sup>4</sup> It is most conveniently prepared by heating phenylbenzoyldiazomethane— a method first described by Schroeter<sup>5</sup> and later used by Staudinger.<sup>6</sup>

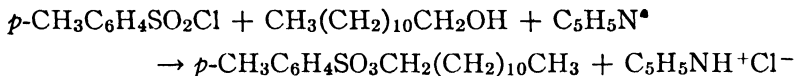
<sup>2</sup> Staudinger, Ber. **44**, 1619 (1911).

<sup>3</sup> Staudinger, *ibid.* **38**, 1735 (1905).

<sup>4</sup> Staudinger, *ibid.* **40**, 1148 (1907).

<sup>5</sup> Schroeter, *ibid.* **42**, 2346 (1909).

<sup>6</sup> Staudinger, *ibid.* **44**, 1623 (1911).

***n*-DODECYL (LAURYL) *p*-TOLUENESULFONATE**

Submitted by C. S. MARVEL and V. C. SEKERA.

Checked by C. F. H. ALLEN and C. V. WILSON.

**1. Procedure**

IN a 1-l. three-necked flask fitted with a stirrer and thermometer are placed 93 g. (0.5 mole) of dodecanol (Note 1) and 158 g. (2 moles) of pyridine. The flask is surrounded by a water bath sufficiently cold to lower the temperature of the mixture to 10°. At this temperature 105 g. (0.55 mole) of *p*-toluenesulfonyl chloride is added in portions over a twenty- to thirty-minute period, or at such a rate that the temperature does not exceed 20° at any time. The mixture is then stirred for three hours at a temperature below 20°, after which it is diluted with 300 cc. of hydrochloric acid (sp.gr. 1.19) in 1 l. of ice water. The ester which crystallizes is collected on a chilled Büchner funnel and sucked as dry as possible. The solid is transferred to a 600-cc. beaker, 250–300 cc. of methyl alcohol is added, and the mixture is warmed on the steam bath until the ester melts. It is then cooled in a freezing mixture while being stirred continuously; the ester separates in a fairly fine state. It is then collected on a chilled funnel and allowed to dry in the air, preferably at a temperature below 20°. The yield of ester is 152–156 g. (88–90 per cent of the theoretical amount based upon the dodecanol used). It melts at 20–25° (Note 2) and is sufficiently pure for most purposes.

If a purer product is desired, it is recrystallized from petroleum ether (b.p. 30–60°), using 4 cc. per 3 g., and drying over anhydrous sodium sulfate. The solution is chilled to 0° and the ester filtered on a chilled funnel; the recovery is 90 per cent, and the melting point is 28–30°. Evaporation of the solvent to a small volume deposits an additional amount (Note 3).

## 2. Notes

1. Dodecanol (lauryl alcohol), m. p. 22–22°; pyridine, b.p. 113–115°; and *p*-toluenesulfonyl chloride, m.p. 66–68°, are used.

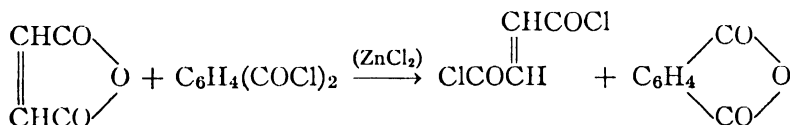
2. The ester contains traces of water, which makes the melting point unreliable; the freezing point is 24–25°.

3. The following esters have been made in essentially the same yields: butyl *p*-toluenesulfonate (Org. Syn. Coll. Vol. 1, 139); *n*-tetradecyl *p*-toluenesulfonate, m.p. 35°; *n*-hexadecyl *p*-toluenesulfonate, m.p. 49°; *n*-octadecyl *p*-toluenesulfonate, m.p. 56°; *n*-decyl *p*-bromobenzenesulfonate, m.p. 43–44°; *n*-dodecyl *p*-bromobenzenesulfonate, m.p. 49°; *n*-tetradecyl *p*-bromobenzenesulfonate, m.p. 51.5°; *n*-hexadecyl *p*-bromobenzenesulfonate, m.p. 60°; *n*-octadecyl *p*-bromobenzenesulfonate, m.p. 64–65°.

## 3. Method of Preparation

*n*-Dodecyl *p*-toluenesulfonate has been prepared only by the action of *p*-toluenesulfonyl chloride on dodecanol-1 in the presence of pyridine<sup>1</sup> according to the general procedure developed by Patterson and Frew<sup>2</sup> for making esters of sulfonic acids.

## FUMARYL CHLORIDE



Submitted by L. P. KYRIDES.

Checked by C. F. H. ALLEN and F. P. PINGERT.

## 1. Procedure

A MIXTURE of 98 g. (1 mole) of maleic anhydride, m.p. 52–54°, 230 g. of commercial phthaloyl chloride (Note 1), and 2 g.

<sup>1</sup> Sekera and Marvel, J. Am. Chem. Soc. **55**, 345 (1933).

<sup>2</sup> Patterson and Frew, J. Chem. Soc. **89**, 332 (1906).

of anhydrous zinc chloride is placed in a 500-cc. three-necked, round-bottomed flask. The flask is provided with a thermometer, the bulb of which extends into the liquid nearly to the bottom, and an efficient fractionating column (Notes 2, 3, and 4). A 500-cc. water-cooled distilling flask is connected to the side arm of the column to serve as a receiving vessel.

The reaction mixture is heated by means of an oil bath (inside temperature  $130-135^{\circ}$ ) for two hours, taking care to avoid overheating (Note 5), and then allowed to cool to  $90-95^{\circ}$ . The fumaryl chloride is distilled as rapidly as possible (twenty minutes), and the portion boiling over a  $25^{\circ}$  range ( $60-85^{\circ}/13-14$  mm.) is collected. It is then redistilled slowly (one hour), and the portion boiling over a  $2^{\circ}$  range ( $62-64^{\circ}/13$  mm.) is collected (Note 6). The yield is 125-143 g. (82-95 per cent of the theoretical amount) (Notes 7 and 8).

## 2. Notes

1. Commercial phthaloyl chloride contains about 94 per cent of halide and some phthalic anhydride. The amount of chloride specified corresponds to a slight molar excess.

2. The checkers employed a modified Widmer column<sup>1</sup> (Fig. 4) that has been used in many organic laboratories, but not officially described. They also used a Vigreux column (50 cm. effective length, 2.7 cm. inside diameter); the first distillation then required ninety minutes, and the yield was 82-83 per cent. The final temperature of the reaction mixture and observed boiling point will depend upon the type of apparatus used.

3. This procedure has also been checked using a fractionating column 30 cm. in length and 1.5 cm. in inside diameter packed with glass Wilson rings<sup>2</sup> and provided with the usual jackets for electrical heating. The distillation requires three hours. If this column is used, a single distillation gives a product pure enough for most purposes. An unpacked, indented column of about the same dimensions was unsatisfactory (checked by N. L. Drake).

<sup>1</sup> Widmer, *Helv. Chim. Acta* **7**, 59 (1927).

<sup>2</sup> Wilson, Parker, and Laughlin, *J. Am. Chem. Soc.* **55**, 2795 (1933).



4. Rubber stoppers are used throughout. Tightly fitting ground-glass connections are convenient but unnecessary. The third neck of the flask is used when acid chlorides are prepared from the corresponding acids (Note 9).

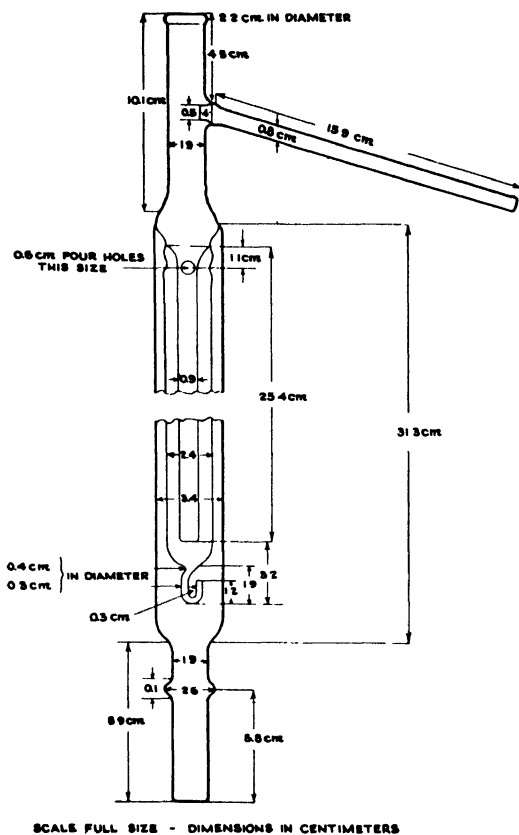


FIG. 4.

5. Above 135° the reaction is likely to get out of control; the ensuing decomposition seriously reduces the yield. For this reason the flask should be immersed only slightly in the oil bath (about one-third of the depth of the liquid layer).

6. With some lots of phthaloyl chloride, owing to the presence of an unknown impurity, the first few drops of the distillate have a reddish color. If the distillation is interrupted and air admitted

to the system, the same phenomenon is observed on resuming the distillation.

7. The yield obtained is usually nearer the higher figure. The checkers carried out this preparation using five times these amounts and a 3-l. flask. The distillation times were one hour for the first and three hours for the final distillation.

8. Fumaryl chloride is best preserved in sealed glass containers. Bottles, closed by rubber stoppers free from sulfur, can be used for short periods. Ground glass-stoppered bottles are unsuitable, the joints readily becoming "frozen," owing to hydrolysis of the chloride.

9. According to the submitters, yields of the order of 95 per cent of other acid chlorides can be obtained by the use of phthaloyl chloride (1 mole of chloride to 1 mole of a monobasic acid, 2 moles of chloride to 1 mole of a dibasic acid). Zinc chloride, as catalyst, is not necessary in the reaction of most acids and their anhydrides with phthaloyl chloride. When acids are used, it is best to add one of the components slowly, in order to avoid a too violent evolution of hydrogen chloride on warming.

### 3. Methods of Preparation

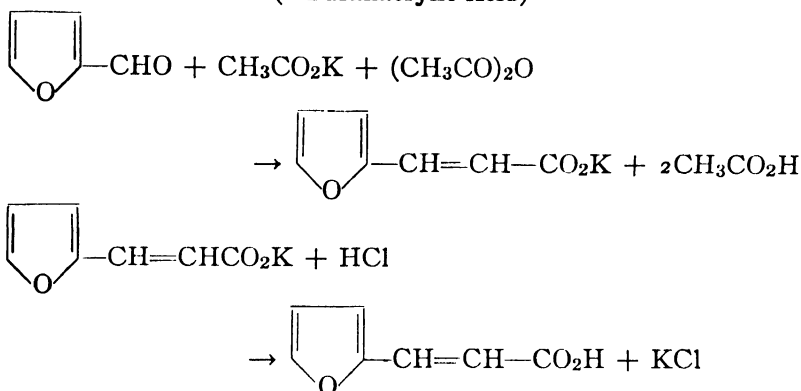
Fumaryl chloride has been prepared from fumaric acid and phthaloyl chloride,<sup>3</sup> from maleic acid by the action of thionyl chloride in the presence of zinc chloride, and from maleic anhydride by the use of phthaloyl chloride in the presence of zinc chloride.<sup>4</sup>

<sup>3</sup> Van Dorp and Van Dorp, *Rec. trav. chim.* **25**, 96 (1906).

<sup>4</sup> Kyrides, *J. Am. Chem. Soc.* **59**, 207 (1937).

## FURYLACRYLIC ACID

## (2-Furanacrylic Acid)



Submitted by JOHN R. JOHNSON.

Checked by R. L. SHRINER and C. M. STEVENS.

## 1. Procedure

IN a 3-l. round-bottomed flask provided with a mechanical stirrer and a 90-cm. air-cooled condenser are placed 288 g. (3 moles) of freshly distilled furfural, 460 g. (425 cc., 4.5 moles) of acetic anhydride, and 294 g. (3 moles) of dry, pulverized, freshly fused potassium acetate (Note 1). The ingredients are mixed thoroughly, stirring is started, and the flask is heated in an oil bath at 150° (bath temperature) for four hours, without interruption (Note 2). It is well to make provision for acetic acid vapor which escapes through the air condenser.

After cooling slightly, the reaction mixture is transferred to a large flask and treated with 3.5 l. of water. Part of this is used to rinse out the reaction flask. The mixture is boiled with 30 g. of Norite for about ten minutes and is filtered while still *hot* with suction, using a preheated Büchner funnel. Furylacrylic acid tends to separate quickly and sometimes offers trouble in clogging the funnel. The filtrate is acidified to Congo red by the addition of a 1:1 solution of concentrated hydrochloric acid in water.

After being cooled to  $20^{\circ}$  or below, preferably with stirring, and being allowed to stand for at least one hour, the acid is filtered with suction and washed with a small quantity of ice water. The yield is 270–290 g. (65–70 per cent of the theoretical amount). The light tan crude acid melts at  $138\text{--}139^{\circ}$  (Note 3).

## 2. Notes

1. If fused sodium acetate is used the reaction is slower and six to eight hours' heating is required.

2. When the temperature of the bath approaches  $145\text{--}150^{\circ}$  a rapid exothermic reaction sets in. This must be controlled (by application of cold wet towels to the flask) to avoid too vigorous ebullition.

3. Furylacrylic acid melting at  $138\text{--}139^{\circ}$  is sufficiently pure for most purposes. The acid is perfectly white when pure, but many recrystallizations are required to attain that state. It may be recrystallized from benzene or ligroin ( $90\text{--}100^{\circ}$ ) with the addition of Norite. The loss is about 20–25 per cent, and the product melts at  $139\text{--}140^{\circ}$  (sometimes  $140\text{--}141^{\circ}$ ).

## 3. Methods of Preparation

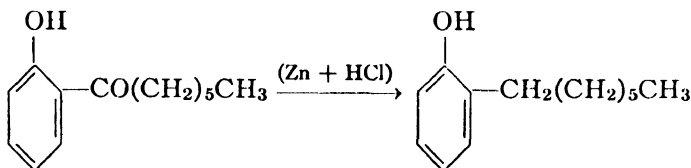
Furylacrylic acid has usually been prepared from furfural by the Perkin reaction.<sup>1</sup> The use of potassium acetate is advantageous, since it allows the reaction to proceed rapidly at relatively lower temperatures. The acid has also been prepared from furfural and malonic acid in the presence of pyridine,<sup>2</sup> and by oxidation of furfuralacetone with bleaching powder.<sup>3</sup>

<sup>1</sup> Baeyer, *Ber.* **10**, 357 (1877); Marckwald, *ibid.* **20**, 2812 (1887); Gibson and Kahnweiler, *Am. Chem. J.* **12**, 314 (1890).

<sup>2</sup> Dutt, *J. Indian Chem. Soc.* **1**, 297 (1925) [*C. A.* **19**, 2475 (1925)].

<sup>3</sup> Hurd and Thomas, *J. Am. Chem. Soc.* **55**, 1646 (1933).

## o-n-HEPTYLPHENOL



Submitted by R. R. READ and JOHN WOOD, JR.

Checked by W. E. BACHMANN and M. C. KLOETZEL.

## 1. Procedure

IN a 1-l. three-necked flask fitted with a stirrer (Note 1) and a reflux condenser is placed 200 g. of amalgamated mossy zinc (Note 2). A mixture of 200 cc. of water and 200 cc. of concentrated hydrochloric acid is added and then a solution of 60 g. of *o*-heptanoyl phenol (Note 3) in 100 cc. of alcohol. The mixture is agitated vigorously and refluxed until reduction is complete (Note 4).

To the mixture is added 120 cc. of toluene, stirring being continued for a few minutes. The toluene solution is separated from the aqueous solution and washed three times with water. The solution is filtered from suspended matter, and the toluene is distilled from a Claisen flask until a thermometer in the liquid reads 170° (Note 5). The residue is then distilled *in vacuo*, the portion boiling at 118–123° at 1 mm. being collected (Note 6). The yield of colorless *o*-*n*-heptylphenol is 45–47 g. (81–86 per cent of the theoretical amount) (Note 7).

## 2. Notes

1. The stirrer should be as large and substantial as the flask will accommodate, since the rate of reduction depends greatly on complete emulsification of the oil.

2. The zinc is amalgamated in the reaction flask by covering it with a solution of 4 g. of mercuric chloride in 300 cc. of water. Occasional agitation during one-half hour is sufficient for amal-

gamation. The solution is poured off, and the zinc is rinsed once with water.

3. *o*-Heptanoyl phenol may be prepared by the method of Miller and Hartung (Org. Syn. 13, 90). The checkers found that, by keeping the mixture of *ortho* and *para* isomers in a cool place overnight, most of the *para* isomer crystallized and could be separated by filtration. The *ortho* isomer is then obtained by fractional vacuum distillation, repeated two or three times. *o*-Heptanoyl phenol boils at 135–140° at 3 mm.; *p*-heptanoyl phenol boils at 200–207° at 4 mm.

4. The reduction requires at least eight hours and may take twice that long. For testing completeness of reduction, 0.1 cc. of the oil is withdrawn and dissolved in 2 cc. of alcohol; to the solution is added 2–4 drops of a 10 per cent solution of ferric chloride in alcohol. A deep red or reddish-brown color is produced by the ketone; a light brownish-yellow color indicates completion of the reduction. A standard solution containing 0.5 g. of the ketone per liter of alcohol is used for comparison, 2 cc. of this solution being treated with a few drops of the ferric chloride solution. Since the *para* acylphenols usually do not give a pronounced color with ferric chloride, at least eight hours should be allowed for their reduction.

5. Drying of the toluene extract is unnecessary, since the water is carried over during the removal of the toluene. If necessary, the toluene may be returned once to the flask to effect complete removal of the water.

6. The residue from the distillation is usually less than 5 g. and may be discarded.

7. Other ketones may be reduced by this same procedure. The submitters report that the following have been reduced with yields of 70–90 per cent: *o*- and *p*-butyryl phenols, *o*- and *p*-valeryl phenols, *o*- and *p*-caproyl phenols, *o*- and *p*-heptanoyl phenols, *o*- and *p*-octanoyl phenols, *o*- and *p*-pelargonyl phenols, *o*- and *p*-undecyllyl phenols. The same procedure applies to acyl resorcinols and acyl chlororesorcinols. Caproyl and octanoyl resorcinols reduce to the corresponding alkyl derivatives in yields of 70–80 per cent. Butyryl, valeryl, caproyl, heptanoyl,

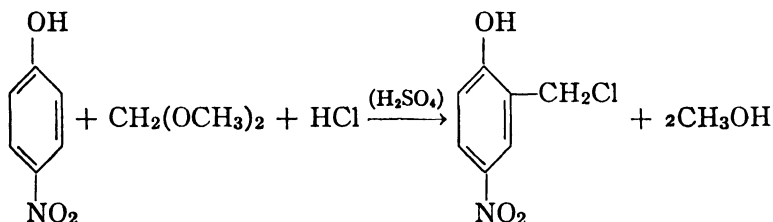
and octanoyl chlororesorcinols reduce to the corresponding alkyl chlororesorcinols in yields of 60–75 per cent.

### 3. Methods of Preparation

Primary alkyl phenols have been prepared by the reduction of acyl phenols;<sup>1</sup> by the demethylation of the corresponding ethers;<sup>1,2</sup> by the diazotization of the corresponding amines;<sup>3</sup> and by the alkali fusion of sulfonates.<sup>4</sup> Alkyl resorcinols have been prepared by the reduction of acyl resorcinols.<sup>1,5,6</sup> Alkyl chlororesorcinols have been prepared from the corresponding acyl chlororesorcinols by reduction.<sup>7</sup>

### 2-HYDROXY-5-NITROBENZYL CHLORIDE

(Toluene,  $\alpha$ -Chloro-2-hydroxy-5-nitro-)



Submitted by C. A. BUEHLER, FRED K. KIRCHNER and GEORGE F. DEEBEL.

Checked by C. F. H. ALLEN and ALAN BELL.

### 1. Procedure

In a 1-l. three-necked, round-bottomed flask equipped with a mechanical stirrer, short reflux condenser, and bent glass tube

<sup>1</sup> Johnson and Hodge, J. Am. Chem. Soc. **35**, 1014 (1913); Coulthard, Marshall, and Pyman, J. Chem. Soc. (1930), 280.

<sup>2</sup> Klages, Ber. **32**, 1438 (1899).

<sup>3</sup> Org. Syn. Coll. Vol. **1**, 128, 407.

<sup>4</sup> Ullmann, "Enzyklopädie der technischen Chemie," Vol. 9, p. 35, Urban and Schwarzenberg, Berlin, 1921.

<sup>5</sup> Johnson and Lane, J. Am. Chem. Soc. **43**, 348 (1921).

<sup>6</sup> Dohme, Cox, and Miller, *ibid.* **48**, 1688 (1926).

<sup>7</sup> Read, Reddish, and Burlingame, *ibid.* **56**, 1377 (1934).

reaching below the surface of the liquid for the introduction of hydrogen chloride, are placed 50 g. (0.36 mole) of *p*-nitrophenol (Note 1), 650 cc. of concentrated hydrochloric acid, 5 cc. of concentrated sulfuric acid (Note 2), and 76 g. (1 mole) of methylal (Note 3). The mixture is stirred while the temperature is maintained at  $70 \pm 2^\circ$  for four to five hours by means of a water bath (Note 4). During this time hydrogen chloride is bubbled into the reaction mixture through the bent glass tube, and the excess gas is carried away through the reflux condenser to a hood or gas-absorption trap (Org. Syn. 14, 2) (Note 5).

The 2-hydroxy-5-nitrobenzyl chloride begins to separate as a solid about one hour after the beginning of the reaction. At the end the mixture is cooled in ice for one hour whereby more crystals separate, after which the acid liquors are either filtered or decanted from the crystals (Note 6). The 2-hydroxy-5-nitrobenzyl chloride is purified by recrystallization from 125 cc. of hot benzene (Note 7). The yield is 46 g. (69 per cent of the theoretical amount based on *p*-nitrophenol) of a white product melting at  $129-130^\circ$ .

## 2. Notes

1. Best results are obtained by using *p*-nitrophenol of a grade melting above  $112^\circ$ .

2. The reaction will proceed in the absence of sulfuric acid, but in its presence a greater reaction velocity results.

3. Methylal, used in excess, is prepared according to the method given by Houben.<sup>1</sup> Twelve hundred grams of methyl alcohol is added to 800 g. of anhydrous calcium chloride in a 5-l. round-bottomed flask equipped with a reflux condenser. Twenty-four grams of concentrated hydrochloric acid is added, and then, with cooling, 800 g. of technical 35-40 per cent formaldehyde is slowly dropped in through a dropping funnel. The reaction is strongly exothermic, requiring about two hours for complete addition of the formaldehyde. When all the formaldehyde has been added, the mixture is heated with a Bunsen flame

<sup>1</sup> Houben, "Die Methoden der organischen Chemie," 3rd Ed., Vol. III, p. 193, Verlag Georg Thieme, Leipzig, 1930.



for a few minutes until the liquid boils vigorously. The methylal forms quickly as an upper layer and, after six hours' standing, is fractionally distilled, preferably using a Clarke and Rahrs column.<sup>2</sup> The 42-46° fraction is sufficiently pure for use.

4. Temperatures higher than 72° may result in the formation of oily-resinous material with a corresponding decrease in chloride. The reaction is nearly complete at the end of four hours, but additional time will result in a slightly increased yield.

5. Rubber joints should be used sparingly as the hydrogen chloride causes an internal swelling of the rubber with subsequent blocking of the lines.

6. The high acid concentration makes ordinary filtration difficult. By allowing the reaction mixture to stand in an ice bath for one hour, the solid clings together, and filtration with gentle suction or decantation can be used with ease.

7. The solid material should be air-dried for several hours or, better, overnight to remove all water before recrystallizing from hot benzene. The chlorine atom is very labile and hydrolyzes easily to form 2-hydroxy-5-nitrobenzyl alcohol.

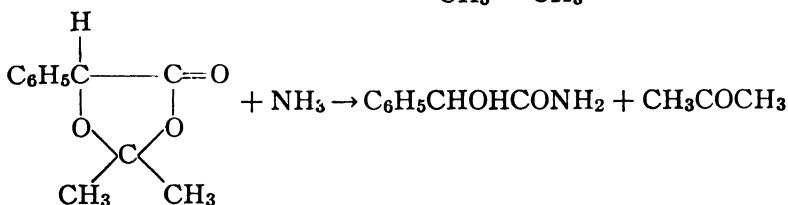
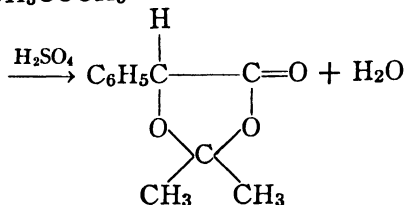
### 3. Methods of Preparation

2-Hydroxy-5-nitrobenzyl chloride can also be prepared from 2-hydroxy-5-nitrobenzyl alcohol by passing hydrogen chloride into an alcoholic solution at  $70 \pm 2^\circ$  for two hours. In this case the yield of chloride is almost quantitative. The foregoing detailed procedure has been arrived at from that given in German Patent 132,475.<sup>3</sup>

<sup>2</sup> Clarke and Rahrs, *Ind. Eng. Chem.* **18**, 1092 (1926).

<sup>3</sup> *Fr. dl.* **6**, 142 (1904).

## MANDELAMIDE



Submitted by L. F. AUDRIETH and M. SVEDA.

Checked by HOMER ADKINS and WILLIAM H. BATEMAN.

## 1. Procedure

ONE HUNDRED AND FORTY-SIX grams (0.96 mole) of mandelic acid is dissolved in 440 cc. (6.2 moles) of acetone, and the resulting solution is placed in a 2-l. three-necked flask fitted with an efficient stirrer, a dropping funnel, and a thermometer. The reaction flask is placed in an ice-salt bath, and 98 g. of concentrated sulfuric acid (sp. gr. 1.84) is added through the dropping funnel at such a rate that the temperature does not exceed  $-10^\circ$ . The reaction mixture is then poured into an ice-cold solution of sodium carbonate containing 200 g. of the anhydrous salt in 1800 cc. of water. The mandelic acid-acetone condensation product precipitates from the solution. The curdy product is washed by grinding with ice water (200 cc.) and is then filtered and dried over calcium chloride under reduced pressure. The crude product weighs 181 g. (Note 1).

The mandelic acid-acetone condensation product is added in small portions to about 1800 cc. of liquid ammonia (Note 2) contained in two silvered 1-l. Dewar flasks. Each flask is fitted with

a stopper containing a capillary tube to serve as an ammonia outlet. The ammonolysis is allowed to proceed overnight, after which the contents of the flasks are poured into open beakers to facilitate rapid evaporation of the liquid ammonia.

After the ammonia has been removed to a point where a pulverulent mass remains, the product is treated with 475 cc. of hot absolute alcohol and the resulting solution is filtered through a hot funnel to remove insoluble impurities. The filtrate is cooled in an ice bath to give about 90 g. of glistening white crystals of mandelamide melting at  $132^{\circ}$  (62 per cent of the theoretical amount based upon the mandelic acid) (Notes 3 and 4).

## 2. Notes

1. The crude product contains varying quantities of sodium carbonate and sodium sulfate, which are difficult to remove. These impurities are insoluble in liquid ammonia; consequently the crude compound can be ammonolyzed without further purification. The mandelic acid-acetone condensation product may be purified by recrystallization from absolute alcohol; it then melts at  $45^{\circ}$ .

2. The solubility of the mandelic acid-acetone condensation compound in liquid ammonia at its boiling point is approximately 10 g. per 100 cc.

3. Additional quantities of mandelamide may be obtained by concentrating the alcoholic mother liquor carefully.

4. This method is generally applicable to the preparation of the amides of  $\alpha$ -hydroxy acids.

## 3. Methods of Preparation

Mandelamide has been prepared by treating the ethyl ester with concentrated aqueous ammonia,<sup>1,2</sup> and a saturated alcoholic solution of ammonia has been used to effect ammonolysis of the methyl ester.<sup>3</sup> Esters of mandelic acid were treated with liquid

<sup>1</sup> Beyer, J. prakt. Chem. (2) **31**, 390 (1885).

<sup>2</sup> Einhorn and Feibelmann, Ann. **361**, 145 (1908).

<sup>3</sup> McKenzie and Wren, J. Chem. Soc. **93**, 311 (1908)

ammonia at its boiling point;<sup>4</sup> this procedure was improved by use of ammonia at superatmospheric pressures and higher temperatures.<sup>5</sup> The procedure described in this synthesis was first used by Ôeda.<sup>6</sup>

## METHYL $\beta$ -BROMOPROPIONATE



Submitted by RALPH MOZINGO and L. A. PATTERSON.

Checked by NATHAN L. DRAKE and HOMER CARHART.

### 1. Procedure

SIX HUNDRED AND FIFTY grams of a 60 per cent solution of methyl acrylate in methyl alcohol to which has been added 4 g. of hydroquinone (Note 1) is washed, successively, with 800-cc., 400-cc., and 200-cc. portions of a 7 per cent sodium sulfate solution. The methyl acrylate layer is dried by shaking with 45 g. of anhydrous sodium sulfate for twenty to thirty minutes. The ester is then removed from the sodium sulfate by filtration and used without distillation. The yield is 280-325 g.

A solution of 258 g. (3 moles) of washed and dried methyl acrylate in 500 cc. of anhydrous ether is placed in a 1-l. round-bottomed flask. The flask is fitted with a rubber stopper carrying a drying tube and an 8-mm. glass inlet tube for hydrogen bromide. The inlet tube, which extends almost to the bottom of the flask, is connected through a 1-l. safety trap to a hydrogen bromide generator (Note 2). The flask with its contents is placed in an ice bath, and 245 g. (3.03 moles) of anhydrous hydrogen bromide is passed into the solution (Note 3). After the hydrogen bromide has been added, the flask is stoppered and allowed to stand for about twenty hours at room temperature.

The ether is removed by distillation (Note 4) from a hot water bath. At the end of the distillation, the water bath is

<sup>4</sup> Glattfeld and MacMillan, J. Am. Chem. Soc. **58**, 898 (1936).

<sup>5</sup> Kleinberg and Audrieth, J. Org. Chem. **3**, 312 (1938).

<sup>6</sup> Ôeda, Bull. Chem. Soc. Japan **11**, 385 (1936).

heated to 80–85°, and when no more liquid comes over at this temperature the residue is transferred to a 500-cc. modified Claisen distilling flask and distilled under reduced pressure. The methyl  $\beta$ -bromopropionate distils at 64–66° at 18 mm. and weighs 410–428 g. (80–84 per cent of the theoretical amount) (Notes 5 and 6).

## 2. Notes

1. Methyl acrylate in methyl alcohol is available from Röhm and Haas Company, Philadelphia, Pa. Since the ester polymerizes in the presence of peroxides, it is necessary to add some hydroquinone as an inhibitor. The ester should not be stored for long periods of time, even when it contains hydroquinone. Storage should be in a refrigerator.

2. The hydrogen bromide (Org. Syn. 15, 42) may be completely freed from bromine by bubbling it through a solution of phenol in carbon tetrachloride.

3. The addition may be as rapid as is convenient without the loss of ether due to the exothermic reaction.

4. The ether may be removed under anhydrous conditions and used for a subsequent preparation of the ester without further treatment.

5. Ethyl  $\beta$ -bromopropionate may be prepared in the same manner in about 90 per cent yield. The boiling point of the ethyl ester is 77–79° at 19 mm.

6. The residue consists largely of  $\beta$ -bromopropionic acid which may be recovered by distillation, b.p. 115–120°/18 mm., followed by recrystallization from carbon tetrachloride. The yield of this acid has never been more than 5 per cent of the theoretical amount.

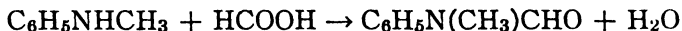
## 3. Methods of Preparation

Methyl  $\beta$ -bromopropionate has been prepared by the esterification of  $\beta$ -bromopropionic acid with methyl alcohol alone<sup>1</sup> and through the use of hydrogen bromide as a catalyst,<sup>2</sup> and by the direct addition of hydrogen bromide to methyl acrylate.<sup>2</sup>

<sup>1</sup> Le Mer and Kamner, J. Am. Chem. Soc. 53, 2833 (1931).

<sup>2</sup> Moureu, Murat, and Tampier, Ann. chim. 15, 221 (1921)

## N-METHYLFORMANILIDE



Submitted by L. F. FIESER and J. E. JONES.

Checked by C. F. H. ALLEN and J. VAN ALLAN.

### 1. Procedure

IN a 3-l. round-bottomed flask fitted with a 3-ft. indented column to which is attached a condenser set for downward distillation are placed 321 g. (3 moles) of methylaniline, 300 g. of formic acid (85-90 per cent), and 1800 cc. of toluene (Note 1). The solution is distilled slowly. As long as the azeotrope containing water is present, the temperature of the vapor is 87-88°; when the water has been removed, the temperature rises to 108-110° (Note 2). The distillation is continued until approximately 1500 cc. of toluene has been collected (five to six hours). The residue is then transferred to a modified Claisen flask (Org. Syn. Coll. Vol. 1, 125) and distilled *in vacuo*, the portion boiling at 114-121° at 8 mm. being collected. This has a freezing point of 13.6-13.7°;  $n_D^{29}$  1.553-1.555. The yield is 380-393 g. (93-97 per cent of the theoretical amount). This product is satisfactory for the preparation of aldehydes (p. 11). Upon redistillation it boils at 117-121° at 8 mm., 130-132° at 22 mm. The freezing point and refractive index are unchanged.

### 2. Notes

1. The toluene serves to remove the water and minimize side reactions.
2. The water layer of the distillate is separated; it amounts to 140-150 cc.

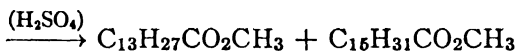
### 3. Methods of Preparation

Methylformanilide has been obtained in a yield of 67.5 per cent by heating methylaniline with formamide in glacial acetic

acid solution.<sup>1</sup> The method above is a modification of that of Morgan and Grist,<sup>2</sup> who heated the amine and formic acid in the absence of a solvent or water-carrier (the present authors obtained a yield of only 40-50 per cent by that procedure).

## METHYL MYRISTATE AND METHYL PALMITATE AND THE CORRESPONDING ACIDS

Bayberry wax + CH<sub>3</sub>OH



Submitted by J. C. SAUER, B. E. HAIN, and P. W. BOUTWELL.

Checked by HOMER ADKINS and ROBERT E. BURKS, JR.

### 1. Procedure

IN a 3-l. round-bottomed flask are placed 500 g. of bayberry wax (Note 1), 600 g. of methanol, and 31 g. of sulfuric acid. Boiling chips are added, and the mixture is refluxed for forty-eight hours on the steam bath. About half of the methanol is removed by distillation, and 500 cc. of water is added to the remaining mixture. The ester layer is separated and washed several times with water. About 500 g. of crude methyl esters is obtained.

The esters are fractionally distilled through a suitable fractionating column (Note 2). A second fractionation is then made so that each successive fraction is added to the distilling flask after the temperature has reached the upper limit for the fraction being collected. There is obtained 170-190 g. of methyl myristate, b.p. 91-94°/0.5 mm., 112-116°/1 mm., or 157-162°/10 mm., and 170-190 g. of methyl palmitate, b.p. 115-118°/0.5 mm., 129-133°/1 mm., or 180-183°/10 mm. (Notes 3, 4, 5, and 6).

<sup>1</sup> Hirst and Cohen, J. Chem. Soc **67**, 830 (1895).

<sup>2</sup> Morgan and Grist, *ibid.* **113**, 690 (1918).

## 2. Notes

1. Bayberry wax, also known as myrtle or laurel wax, is obtained from the berries of various species of *Myrica*. The commercial wax, prepared from the berries of *Myrica cerifera*, may be obtained from chemical supply houses for about \$0.60 per pound. The relative proportions of myristin and palmitin in bayberry wax varies somewhat, but these two compounds constitute about 95 per cent of the wax.

2. Several columns are suitable for this separation. The submitters used a three-ball Snyder column 26 cm. in length (similar to No. 28575 of E. H. Sargent, Chicago), sealed to a 500- or 200-cc. modified Claisen flask. The method of operation was essentially that of Simons and Wagner.<sup>1</sup> The column was not electrically heated but was snugly wrapped with asbestos paper. The rate of distillation was about 20 drops per minute, and the reflux ratio 2 or 3 to 1. Flooding of the column must be carefully avoided. The checkers used a modified Widmer column which carried a spiral, 14 cm. long with eleven turns of the helix, contained in a glass tube 12 mm. in internal diameter. A 500-cc. flask was employed for the first fractionation and a 250-cc. one for the refractionation. The column and the oil bath were heated electrically. A ground-glass joint was used for connecting the flask and column, the design and method of operation being that described by Smith and Adkins.<sup>2</sup> The temperature of the bath and column heater was so adjusted that the rate of distillation was three to four drops per minute, the spiral being well covered with returning liquid.

3. Suitable ranges for taking off fractions at various pressures on the first fractionation are as follows: 6 g., 152–157°/10 mm.; 176 g., 157–160°/10 mm.; 119 g., 160–180°/10 mm.; 126 g., 180–183°/10 mm.; 163 g., 115–123°/1 mm.; 115 g., 123–130°/1 mm.; 141 g., 130–133°/1 mm.; 29 g., below 91.5°/0.5 mm.; 116 g., 91.5–94.5°/0.5 mm.; 71 g., 94.5–115°/0.5 mm.; 170 g., 115–118°/0.5 mm.; 28 g., 118–125°/0.5 mm. Upon refractiona-

<sup>1</sup> Simons and Wagner, J. Chem. Education 9, 122 (1932).

<sup>2</sup> Smith and Adkins, J. Am. Chem. Soc. 60, 662 (1938).



tion cuts were made as follows: 6 g., 152-157°/10 mm.; 161 g., 157-162°/10 mm.; 81 g., 162-171°/10 mm., 64 g., 171-180°/10 mm.; 120 g., 180-183°/10 mm.; 198 g., 112-116°/1 mm.; 72 g., 116-129°/1 mm.; 147 g., 129-133°/1 mm.; 8 g., below 91.5°/0.5 mm.; 172 g., 91.5-94.5°/0.5 mm.; 10 g., 94.5-115.2°/0.5 mm.; 200 g., 115.2-118.2°/0.5 mm.; 25 g., 118.2-125°/0.5 mm. The temperature at which the esters distil varies with the rate of distillation and with the details of construction and operation of the column. The figures given above are intended to suggest the approximate ranges for cutting fractions.

4. This procedure has been used successfully for many years in the preparation of ethyl laurate, caprylate, and myristate by the alcoholysis of coconut oil (1 kg.) in ethanol (1900 g.) with hydrogen chloride (50 g.) as a catalyst.<sup>3</sup> The method differs slightly from the one described above. The alcoholysis is complete after fifteen or twenty hours, and the solution is then neutralized to methyl orange with barium carbonate. The mixture is added to an equal volume of a saturated sodium chloride solution, whereupon 1100-1300 g. of the mixture of crude ethyl esters separates. This mixture of esters is washed with water and fractionated as described above. The yields are approximately 50 g. of ethyl caprylate, 350 g. of ethyl laurate, and 60 g. of ethyl myristate from 1000 g. of coconut oil.

5. The methyl myristate obtained ( $n_D^{25^\circ}$  1.4353) showed a melting point of 19° when at equilibrium with the liquid. The methyl palmitate ( $n_D^{25^\circ}$  1.4391 when supercooled) gave a melting point of 29.5°.

6. Myristic and palmitic acids can be obtained from their esters by the procedure in Org. Syn. Coll. Vol. 1, 371. From 100 g. of methyl myristate is obtained 85-89 g. (90-95 per cent of the theoretical amount) of colorless myristic acid melting at 52-53°. From 100 g. of methyl palmitate is obtained 84-88 g. (90-95 per cent of the theoretical amount) of colorless palmitic acid melting at 62-63°.

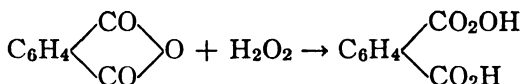
<sup>3</sup> Organic Chemical Reagents, Vol. 3, p. 62, University of Illinois, Urbana, Illinois, 1921.

### 3. Methods of Preparation

Of the early references to the preparation of methyl myristate and methyl palmitate, few are of preparative value. Methyl myristate can be prepared by the fractional distillation of the methyl esters from ucuhuba fat<sup>4</sup> and from cocoanut oil.<sup>5,6</sup> Methyl palmitate can be prepared in a similar manner from cocoanut oil<sup>6</sup> and from bayberry wax.<sup>7</sup>

### MONOPERPHTHALIC ACID

(Phthalic Monoperacid)



Submitted by HORST BÖHME.

Checked by HOMER ADKINS and E. LEON FOREMAN.

#### 1. Procedure

IN a 1-l. round-bottomed flask, equipped with a mechanical stirrer and cooled in an ice-salt bath, is placed 275 g. (250 cc., approximately 1 mole) of 15 per cent sodium hydroxide solution. This is cooled to  $-10^\circ$  (Note 1), and 115 g. (105 cc., approximately 1 mole) of 30 per cent hydrogen peroxide which has been similarly cooled is added in one portion. The heat of reaction causes the temperature to rise markedly. When the temperature has again dropped to  $-10^\circ$ , 75 g. (0.5 mole) of phthalic anhydride which has been pulverized to pass a 40-mesh sieve is added as quickly as possible while the contents are stirred vigorously in the freezing mixture (Notes 2 and 3). As soon as all the anhydride has dissolved, 250 cc. (0.5 mole) of 20 per cent sulfuric acid which has been previously cooled to  $-10^\circ$ , but not frozen (Note 4), is added.

<sup>4</sup> Verkade and Coops, *Rec. trav. chim.* **46**, 528 (1927).

<sup>5</sup> Taylor and Clarke, *J. Am. Chem. Soc.* **49**, 2829 (1927).

<sup>6</sup> Lepkovsky, Feskov, and Evans, *ibid.* **58**, 978 (1936).

<sup>7</sup> Wenzel, *Ind. Eng. Chem. Anal. Ed.* **6**, 1 (1934).

The acid solution is filtered without suction through glass wool into a 2-l. separatory funnel and extracted once with 500 cc. of ether, then three times with 250-cc. portions of the same solvent. The combined ether extracts are shaken out with three 150-cc. portions of 40 per cent ammonium sulfate solution and dried for twenty-four hours, preferably in a refrigerator, over 50 g. of anhydrous sodium sulfate.

If the ether is evaporated under reduced pressure (Note 5), crystalline monoperphthalic acid is obtained. It is more convenient, however, to use the ether solution directly (Note 6). Its peracid content is determined by adding to 2 cc. of the solution 30 cc. of 20 per cent potassium iodide solution and titrating the iodine after ten minutes with 0.05 *N* thiosulfate solution. The yield is 60-65 g. (65-70 per cent of the theoretical amount based on the phthalic anhydride) (Note 7).

## 2. Notes

1. If the solutions are cooled to  $-10^{\circ}$ , little oxygen is evolved, and the yields of peracid are good. If the reaction is carried out at  $0^{\circ}$ , a large amount of oxygen is evolved, and the yields are poor.

2. Commercial phthalic anhydride may be used directly. If excessive decomposition occurs, however, the anhydride should be purified by distillation under reduced pressure.

3. The anhydride is added in large portions or, better, in one portion.

4. The decisive factor in the success of this preparation is the time interval between the addition of the anhydride and the acidification of the reaction mixture. All the anhydride should dissolve, but prolonged stirring results in excessive oxygen evolution. The quicker the anhydride dissolves, and the smaller the oxygen evolution, the better the yield of the peracid. Hence, stirring must be vigorous.

5. If crystalline monoperphthalic acid is desired, it may be prepared conveniently as follows: The dried ether solution is placed in a distilling flask equipped with a capillary tube connected with a drying tube (p. 9), and the flask is connected with

the water pump. The ether is evaporated at the pressure thus obtained without the application of heat (ice will form on the flask) to a thin syrup (approximately 150 cc.). The syrup is transferred to an evaporating dish and the flask rinsed with a small amount of dry ether, the washings being added to the syrup. The remainder of the ether is then evaporated in a vacuum desiccator over concentrated sulfuric acid. For good results in this preparation the drying must be very thorough, for only 1 per cent of water in the ether solution will be more than sufficient to destroy the entire amount of peracid.

6. If ether is not suitable for the oxidation reactions in which the peracid is to be used, the material can be dissolved in another solvent after removal of the ether. An excellent solvent for monoperphthalic acid oxidations is dioxane, and a solution of the peracid in dioxane is readily prepared by adding dioxane to the dried ether extract and then removing the ether under reduced pressure at 15°. The dioxane must be peroxide-free.<sup>1</sup>

7. As originally submitted, this preparation was on one-fifth the scale indicated here. However, the checkers have had no difficulty with the larger-scale preparation.

### 3. Methods of Preparation

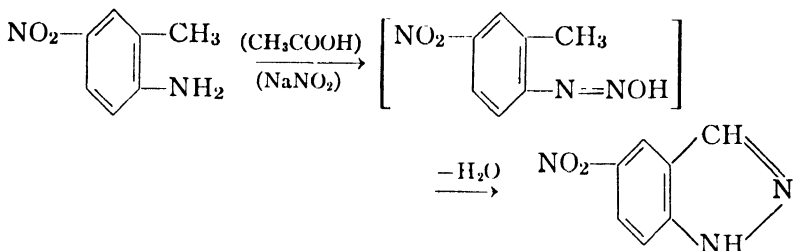
Monoperphthalic acid has been prepared by hydrolysis of phthalyl peroxide with sodium hydroxide<sup>2</sup> and by shaking phthalic anhydride with excess alkaline peroxide solution.<sup>2</sup> The method described here is a modification of this latter process.<sup>3</sup>

<sup>1</sup> Eigenberger, *J. prakt. Chem.* (2) **130**, 75 (1931).

<sup>2</sup> Baeyer and Villiger, *Ber.* **34**, 764 (1901).

<sup>3</sup> Böhm, *ibid.* **70**, 379 (1937).

## 5-NITROINDAZOLE



Submitted by H. D. PORTER and W. D. PETERSON  
 Checked by N. L. DRAKE and A. F. FREEMAN.

## 1. Procedure

To a solution of 55 g. (0.36 mole) of 2-amino-5-nitrotoluene (m.p. 129–132°) in 2500 cc. of glacial acetic acid in a 5-l. round-bottomed flask, provided with an efficient mechanical stirrer, is added all at once (Note 1) a solution of 25 g. (0.36 mole) of sodium nitrite in 60 cc. of water. During this addition the temperature is not allowed to rise above 25° (Note 2). After the nitrite solution has been added, stirring is continued for fifteen minutes to complete the diazotization. Any yellow precipitate formed during the next few hours is filtered and discarded (Note 3).

The solution is allowed to stand for three days at room temperature, and is then concentrated on the steam bath under reduced pressure (water pump) until spattering makes further evaporation impossible. Two hundred cubic centimeters of water is added to the residue, and the contents of the flask are washed into a small beaker where they are stirred to a smooth slurry. The product is filtered, washed thoroughly on the funnel with cold water, and dried in an oven at 80–90°. The crude material melts at 204–206° and weighs 47–57 g. (80–96 per cent of the theoretical amount). It is purified by recrystallization from 650 cc. of boiling methyl alcohol using 5 g. of decolorizing charcoal. The recrystallized, pale yellow needles of 5-nitroindazole melt at 208–209°. The yield is 42–47 g. (72–80 per cent of

the theoretical amount) (Note 4). Further recrystallization does not raise the melting point.

## 2. Notes

1. If the sodium nitrite solution is added slowly, a considerable quantity of a yellow precipitate, presumably the diazoamino compound, is formed.

2. If the solution is cooled in an ice bath to 15–20° before addition of the nitrite solution, the temperature of the mixture will not rise above 25° during the diazotization.

3. This is presumably the diazoamino compound, insoluble in most organic solvents. It melts at about 200°. <sup>1</sup>

4. The unsubstituted *o*-toluidine gives indazole itself, but the yield is very low (3–5 per cent).

## 3. Method of Preparation

The procedure is essentially that of Noelting. <sup>2</sup>

## PENTAACETYL *d*-GLUCONONITRILE



Submitted by H. T. CLARKE and S. M. NAGY.

Checked by W. E. BACHMANN and WAYNE COLE.

## 1. Procedure

To 350 cc. of anhydrous methyl alcohol contained in a 1-l. three-necked, round-bottomed flask, to which is attached a reflux condenser protected by a drying tube, is added 20 g. (0.87 gram atom) of sodium (Note 1) in large pieces. The reaction is kept under control by cooling the flask in a pan of ice water. To the resulting solution of sodium methoxide is added a solution (Note 2) of 61 g. of hydroxylamine hydrochloride

<sup>1</sup> Meunier, Bull. soc. chim. (3) **31**, 641 (1904).

<sup>2</sup> Noelting, Ber. **37**, 2584 (1904).

(0.88 mole) in 20 cc. of water; during the addition the mixture is swirled in order to avoid spattering. After twenty minutes the mixture is cooled to 0° and filtered with suction. The sodium chloride is washed with 350 cc. of anhydrous methyl alcohol. The combined filtrate and washings are warmed to 65° in a 3-l. round-bottomed flask, and a solution of 100 g. of finely powdered commercial crystalline glucose monohydrate (0.50 mole) in 200 cc. of warm 25 per cent aqueous methyl alcohol is added, with stirring. The resulting solution is held at 65° for two hours and then concentrated under reduced pressure until no further distillate is obtained; the residue weighs 155–160 g. The resulting syrup (Note 3) is diluted with 300 cc. of methyl alcohol and again distilled, and this process is repeated once (Note 4).

A mixture of 100 g. of powdered, anhydrous sodium acetate and 677 cc. of 90 per cent acetic anhydride (Note 5) is heated on a steam bath in a 3-l. round-bottomed flask under an efficient reflux condenser. Without interrupting the heating a solution of the syrupy glucose oxime in 50 cc. of glacial acetic acid and 100 cc. of cold acetic anhydride is added through a dropping funnel to the hot mixture (Note 6); this requires about one hour (Note 7). Heating is continued for another hour, and the bulk (380–420 cc.) of the acetic acid and any unchanged acetic anhydride is distilled under reduced pressure from a water bath. The residue is immediately stirred into 2 l. of cold water, stirred occasionally during the first three hours, and allowed to stand overnight.

After the mixture has been chilled to 0°, the brown, crystalline mass is filtered with suction and washed with 500 cc. of water. The solid is dissolved in 300 cc. of hot 95 per cent ethyl alcohol, and the solution is heated with 10–15 g. of Norite for five minutes and filtered with suction. The filtrate is gradually cooled to 0°; the crystals are filtered with suction and washed with 20 cc. of cold alcohol. The weight of the first crop is 90–93 g. A second crop is obtained by concentrating the mother liquor under reduced pressure to 25 cc., boiling the solution with Norite, filtering, and chilling the filtrate to 0°. The total yield of colorless pentaacetyl *D*-glucononitrile melting at 82.5–83.5° is 95–96 g. (50 per cent of the theoretical amount).

## 2. Notes

1. In preparing the free hydroxylamine, a little less than the theoretical amount of sodium is employed to avoid the presence of free alkali in the reaction mixture.

2. The hydroxylamine hydrochloride dissolves in the small amount of water when the mixture is warmed to about 125°.

3. The isolation of glucose oxime is unnecessary in this preparation.

4. The distillation with methyl alcohol serves to remove water almost completely.

5. If acetic anhydride of a higher concentration is available, correspondingly smaller quantities may be employed.

6. The viscous, syrupy glucose oxime dissolves with difficulty, and it may be necessary to warm the mixture slightly. If this is done, a pan of ice water should be at hand in order to cool the mixture should the temperature begin to rise rapidly.

7. In the process described in the literature, the oxime, sodium acetate, and acetic anhydride are allowed to react without dilution, a condition which frequently leads to an uncontrollably violent reaction.

## 3. Methods of Preparation

The above method for preparing glucose oxime is the modification of that of Jacobi<sup>1</sup> developed by Wohl,<sup>2</sup> who first converted the oxime into the pentaacetyl glucononitrile by means of acetic anhydride. The latter reaction was later employed for the same purpose by Zemlén and Kiss.<sup>3</sup>

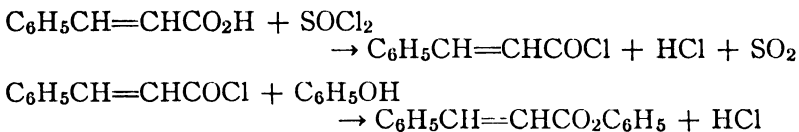
<sup>1</sup> Jacobi, *Ber.* **24**, 696 (1891).

<sup>2</sup> Wohl, *ibid.* **26**, 730 (1893).

<sup>3</sup> Zemlén and Kiss, *ibid.* **60**, 165 (1927).



## PHENYL CINNAMATE



Submitted by ENNIS B. WOMACK and J. McWHIRTER.

Checked by R. L. SHRINER, N. S. MOON, and S. C. KELTON, JR.

## 1. Procedure

A MIXTURE of 148 g. (1 mole) of cinnamic acid and 119 g. (1 mole) of thionyl chloride (Note 1) is placed in a 500-cc. Claisen flask. The side arms are stoppered, and the flask is fitted with a reflux condenser. The apparatus is mounted at an angle so that the condensate will not run into the side arm. To the top of the condenser is attached an exit tube, for evolved hydrogen chloride and sulfur dioxide, leading to a gas-absorption trap (Org. Syn. 14, 2). The mixture is heated on a steam bath, cautiously at first, until no further evolution of hydrogen chloride is noted (forty-five minutes to one hour), and then allowed to cool, and 94 g. (1 mole) of phenol (Note 2) is added. The mixture is again heated on the steam bath until the evolution of hydrogen chloride has ceased (about one hour). It is then placed on a sand bath and brought just to the reflux temperature in order to complete the reaction and remove the hydrogen chloride more completely (Note 3).

The reaction mixture is cooled and distilled under reduced pressure (Note 4). The fraction boiling at 190–210° at 15 mm. is collected. The distillate solidifies to a pale yellow solid melting at 64° to 69° and weighing 186–200 g. (83–89 per cent of the theoretical amount). It is purified by grinding in a mortar to a powder and washing with 500 cc. of cold 2 per cent sodium bicarbonate solution. The residue is recrystallized from 300 cc. of 95 per cent ethyl alcohol. The recovery is 141–168 g. (63–75 per cent) of pure white crystals melting at 75–76°.

## 2. Notes

1. The thionyl chloride should be redistilled before use. The material used in this preparation boiled at  $75.0-75.5^{\circ}$ .

2. The phenol used was Mallinckrodt's analytical reagent grade.

3. A sand-bath temperature of about  $350^{\circ}$  will effect refluxing. Prolonged heating on the sand bath causes considerable loss of product due to decomposition and polymerization and to the conversion of the acid to stilbene by the loss of carbon dioxide.

4. In carrying out the vacuum distillation, it is well not to include the manometer in the system until the unchanged phenol and most of the hydrogen chloride have been removed. Bumping during the distillation may be minimized by holding the burner in the hand and directing the free flame at the surface of the boiling liquid. If the vapors are superheated too much, the boiling-point range may be  $190^{\circ}$  to  $220^{\circ}$  at 15 mm.

## 3. Methods of Preparation

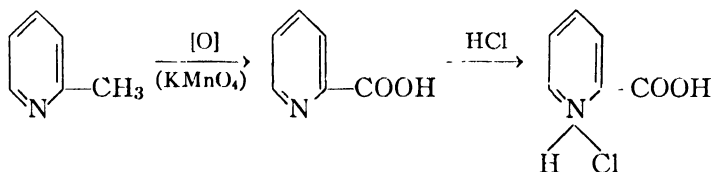
Phenyl cinnamate and other phenolic esters have been prepared by heating the acid and phenol in the presence of phosphorus oxychloride,<sup>1</sup> and by heating the acid anhydride and phenol together in the presence of a dehydrating agent such as fused zinc chloride or anhydrous sodium acetate.<sup>2</sup> Phenyl cinnamate has also been prepared by the careful distillation of phenyl fumarate.<sup>3</sup>

<sup>1</sup> Nencki, *Compt. rend.* **108**, 254 (1889).

<sup>2</sup> Franchimont, *Ber.* **12**, 2059 (1879); Liebermann, *ibid.* **21**, 1172 (1888).

<sup>3</sup> Anschutz, *ibid.* **18**, 1945 (1885).

## PICOLINIC ACID HYDROCHLORIDE



Submitted by ALVIN W. SINGER and S. M. McELVAIN.  
 Checked by C. F. H. ALLEN and ALAN BELL.

## 1. Procedure

IN a 5-l. three-necked flask, fitted with a reflux condenser and stirrer, are placed 2500 cc. of water and 50 g. of  $\alpha$ -picoline (0.54 mole) (Note 1). Ninety grams (0.57 mole) of potassium permanganate is added, and the solution is heated on a steam bath until the purple color has practically disappeared (about one hour). A second 90-g. portion of permanganate is then introduced, followed by 500 cc. of water, and the heating is continued until the purple color is destroyed (two to two and one-half hours). The reaction mixture is allowed to cool slightly, and the precipitated oxides of manganese are filtered and washed well with 1 l. of hot water (Note 2). The filtrate is concentrated *in vacuo* to 150–200 cc., filtered, if necessary, and acidified to Congo red with concentrated hydrochloric acid (65–70 cc., sp. gr. 1.19). This acid solution is then evaporated to dryness *in vacuo*. The solid residue is refluxed for one hour with 250 cc. of 95 per cent alcohol and filtered, and the extraction repeated with 150 cc. of 95 per cent alcohol. Dry hydrogen chloride is passed into the combined alcoholic filtrates until crystals begin to separate. The solution is then chilled to about 10° in a freezing mixture, the addition of hydrogen chloride being continued until the solution is saturated. The crystals of picolinic acid hydrochloride which separate are filtered and air-dried. The yield is 43–44 g. (50–51 per cent of the theoretical amount), m.p. 228–230° (Note 3).

This hydrochloride may contain traces of potassium chloride, which can be removed by dissolving the hydrochloride in hot absolute alcohol (50 g. requires 1 l.) and filtering from insoluble material. An equal volume of dry ether is then added to the warm alcoholic solution, and, after cooling, the crystallized product is filtered. The recovery is 40-43 g., m.p.  $210-212^{\circ}$  ( $230^{\circ}$ ) (Notes 3 and 4).

## 2. Notes

1. The submitters used a picoline fraction, b.p.  $128-132^{\circ}$ , whereas the checkers used the practical product, Eastman Kodak Company, b.p.  $128-134^{\circ}$ . The same yield was obtained with a carefully fractionated picoline, boiling over the  $1^{\circ}$  range  $128-129^{\circ}$ .

2. The washed manganese dioxide does not contain an appreciable amount of acid.

3. When the melting point is determined in the ordinary manner, it is found to be  $228-230^{\circ}$  with decomposition. If, on approaching the melting point, the rate of heating is reduced to  $1^{\circ}$  in five minutes, the value  $210-212^{\circ}$  can be observed.

4. About 2 g. of potassium chloride is removed by this procedure. The unpurified material can be used for most purposes.

## 3. Methods of Preparation

Picolinic acid has been generally prepared by the permanganate oxidation of  $\alpha$ -picoline and isolated through the copper salt.<sup>1,2,3,4,5</sup> In one instance,<sup>6</sup> it was isolated directly as in the present procedure. It has recently been secured by the hydrolysis of  $\omega$ -trichloropicoline.<sup>7</sup>

<sup>1</sup> Weidel, Ber. **12**, 1992 (1879).

<sup>2</sup> Pinner, *ibid.* **33**, 1226 (1900).

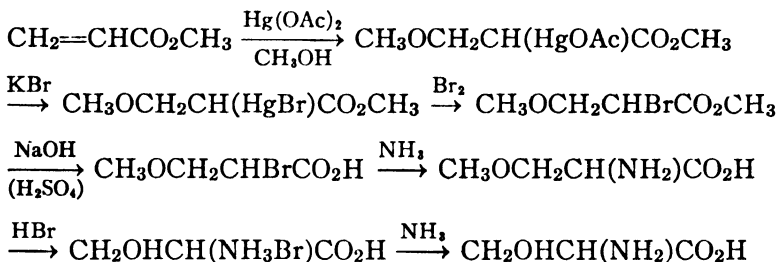
<sup>3</sup> Camps, Arch. Pharm. **240**, 345 (1902).

<sup>4</sup> Ley and Ficken, Ber. **50**, 1132 (1917).

<sup>5</sup> Clemo and Ramage, J. Chem. Soc. (1931), 440.

<sup>6</sup> Mende, Ber. **29**, 2887 (1896).

<sup>7</sup> Dyson and Hammick, J. Chem. Soc. (1939), 781.

**dl-SERINE**

Submitted by HERBERT E. CARTER and HAROLD D. WEST.

Checked by NATHAN L. DRAKE and WILLIAM A. STANTON.

**1. Procedure**

(A) *Methyl  $\alpha$ -Bromo- $\beta$ -methoxypropionate*.—In a 5-l. flask is placed 450 g. of a 60 per cent solution of methyl acrylate in methyl alcohol (Note 1) containing 3.1 moles of methyl acrylate (Note 2). To this solution are added 180 g. of methyl alcohol and 960 g. (3 moles) of mercuric acetate (Note 3). The mixture is allowed to stand at room temperature for three days with occasional shaking (Note 4). The flask is cooled in an ice bath, and a solution of 360 g. (3 moles) of potassium bromide in 1200 cc. of water is added with stirring during fifteen minutes. The heavy oil which separates is extracted with 2.4 l. of chloroform (Note 5), and the aqueous layer is again extracted with 600 cc. of chloroform. The chloroform solutions are combined, washed three times with water, and carefully dried over anhydrous magnesium sulfate (Note 6).

The solution, filtered to remove the drying agent, is placed in a 4-l. beaker and warmed to 50°. The beaker is then exposed to direct sunlight (Note 7), and 450 g. (2.81 moles) of bromine is added with stirring (Note 8) as fast as it is used. The reaction starts slowly but accelerates rapidly, and considerable heat is evolved. The temperature of the solution should be kept below 55° (Note 9). The bromination usually requires twenty to thirty minutes. At the conclusion of the reaction, the flask is cooled

for fifteen minutes in an ice-salt bath, and the mercuric bromide is separated by filtration. The chloroform is removed by distillation under reduced pressure through a 20-in. column, and the residue is fractionally distilled under reduced pressure from a modified Claisen flask (Org. Syn. Coll. Vol. 1, 125). The yield is 480–510 g. (81–86 per cent of the theoretical amount based on the mercuric acetate) of a product boiling at 70–80° at 6 mm. This material contains 5–10 per cent of methyl  $\alpha,\beta$ -dibromopropionate, which is not readily removed. Since the impurity causes no trouble in the synthesis of serine, the crude bromo ester is used in succeeding steps (Note 10).

(B)  *$\alpha$ -Bromo- $\beta$ -methoxypropionic Acid*.—Eight hundred grams of the bromo ester and 1 l. of 0.5 *N* sodium hydroxide are placed in a 5-l. three-necked flask equipped with an efficient stirrer and a separatory funnel, and cooled with running tap water. The stirrer is started, and 800 cc. of 5 *N* sodium hydroxide is added during the course of two hours. After the addition is complete, the solution is stirred for one hour and then neutralized with an equivalent quantity of sulfuric acid (Note 11). The neutralized solution is extracted once with a 1-l. portion, and three times with 500-cc. portions, of ether. The ether extracts are combined, washed once with a cold saturated solution of sodium sulfate, and dried over anhydrous sodium sulfate; the ether is removed by distillation (Note 12). There remains 700–750 g. of crude bromo acid which is used without purification in the preparation of serine (Note 13).

(C) *dl-Serine*.—One-half (350–375 g.) of the crude bromomethoxypropionic acid prepared from the saponification of 800 g. of methyl  $\alpha$ -bromo- $\beta$ -methoxypropionate is heated with 3.5 l. of concentrated ammonium hydroxide in a glass-lined autoclave (Note 14) for ten to fifteen hours at 90–100°, and the solution from the bomb is concentrated to a thick syrup under reduced pressure (Note 15). Two liters of water is added, and the solution is concentrated to dryness. The cake is dissolved in 1.5 l. of 48 per cent hydrobromic acid and refluxed for two and one-half hours. The resulting dark solution is concentrated to a volume of about 500 cc. and then cooled under the tap. The

precipitated ammonium bromide is removed by filtration, and the filtrate is concentrated to a thick syrup (Note 16). One liter of water is added, and the solution is again concentrated to a thick syrup. The syrupy residue is dissolved in 375 cc. of warm water, and ammonium hydroxide is added carefully until a faint odor of ammonia persists after vigorous shaking. One and one-half liters of absolute alcohol is then added slowly (Note 17), and the mixture is allowed to stand overnight. The crude serine is filtered and the filtrate discarded. The precipitate is dissolved in 500 cc. of boiling water (Note 18), heated on the steam cone for ten minutes with 10–15 g. of Darco (Note 19), and then filtered. One-half liter of absolute alcohol is added to the filtrate slowly with stirring. The mixture is cooled to 0° and is kept at this temperature for one hour with occasional stirring to ensure formation of a finely divided precipitate (Note 20). The serine is filtered, washed with alcohol and ether, and air-dried. The precipitates from several runs may be combined and recrystallized as above from 50 per cent alcohol until a white product is obtained (one or two recrystallizations).

All the filtrates should be combined and evaporated to dryness under reduced pressure, and the residue should be recrystallized as above. The last concentrates (including filter paper and Darco washings), if quite dark, may be precipitated from 70 per cent alcohol before recrystallizing. By this process a nearly quantitative recovery may be effected.

The over-all yield is 30 to 40 per cent of the theoretical amount based on the mercuric acetate (Note 21).

## 2. Notes

1. The solution of methyl acrylate in methyl alcohol was obtained from Röhm and Haas Company.

2. If the methyl acrylate solution has stood for some time, it is advisable to use a 10 per cent excess, since the solution slowly deteriorates. A low yield of bromo ester is usually caused by insufficient methyl acrylate.

3. Six hundred and forty-eight grams (3 moles) of mercuric

oxide and 345 cc. (360 g., 6 moles) of acetic acid may be used just as satisfactorily as mercuric acetate. The solution of these substances should be cooled in an ice bath and vigorously shaken for several minutes after the reagents have been mixed, since the reaction of mercuric oxide with acetic acid produces considerable heat.

4. At this time there is still a small amount of undissolved mercuric acetate (and mercuric oxide, if used). Longer standing does not improve the yield.

5. All solutions of the mercury compounds should be handled with care, as they are extremely vesicant to some individuals.

6. The brominations proceed more smoothly if the chloroform solution is washed free of methyl alcohol and dried.

7. The bromination may be carried out just as satisfactorily with the light from two No. 2 Photoflood lamps. These lamps should be mounted in suitable reflectors as near the surface of the solution as possible. The time required may be slightly longer.

8. An efficient mechanical stirrer is required. Near the end of the bromination the precipitate of mercuric bromide becomes quite heavy.

9. The temperature may be controlled by passing tap water through an 8-mm. glass cooling coil mounted in the beaker. The bromination proceeds rapidly at 45–55°, rather slowly at 35–40°, and practically ceases below 30°.

10. The crude ester may be used directly in the preparation of serine. However, greater ease of purification and slightly better yields make it advantageous to prepare the free acid. Pure methyl  $\alpha$ -bromo- $\beta$ -methoxypropionate is obtained by fractionally distilling the crude material under reduced pressure through a Widmer column. From 100 g. of crude material there is obtained 80–90 g. of pure ester, b.p. 73–75°/6 mm.,  $n_D^{20}$  1.4586.

11. It is advisable to keep the temperature below 30° during both the hydrolysis and neutralization.

12. The acid should not be heated for long periods. The last traces of ether should be removed under reduced pressure.

13. The crude bromo acid on standing two or three days may deposit an amorphous solid which is probably a polymerization



product of  $\alpha$ -bromoacrylic acid. If this is removed before the bromo acid is aminated, the subsequent purification of serine is much easier.

14. The checkers employed a simple autoclave, constructed as follows: A piece of 10-in. steam pipe 11 in. long and threaded at both ends was closed at one end by a standard pipe cap. A standard flange was screwed to the other end, and a blank companion flange seating on an "ammonia gasket" provided the closure for the top of the autoclave. A Pyrex battery jar 10 in. high and 8.5 in. in diameter fitted loosely in the pipe and was protected from breakage due to contact with the sides and bottom of the pressure vessel by rings made of rubber tubing. The battery jar was covered with a loosely fitting germinating dish to prevent condensate from the top from dripping into the reaction mixture. After the bromo acid had been introduced into the battery jar, concentrated ammonia was poured into the annular space between the jar and the pipe to provide better heat transfer. The autoclave was heated in a wash tub containing water which was kept boiling by a steam coil.

15. All the concentrations under reduced pressure required in this preparation were carried out with the aid of an efficient water pump.

16. The distillate may be redistilled at atmospheric pressure to recover the hydrobromic acid.

17. Absolute alcohol (200 cc.) is added to the warm (60–70°) solution, and the sides of the flask are scratched to induce crystallization; the remainder of the alcohol is then added in large portions with stirring over a period of one hour.

18. Pure *dl*-serine is soluble in water to the extent of 50 g. per liter at 25°, 200 g. at 80°, and approximately 30 g. at 5–10°. The presence of impurities, however, will increase its solubility greatly.

19. Norite is not so satisfactory as Darco.

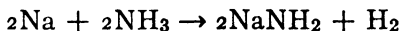
20. Slow precipitation tends to give large crystals with resulting inclusion of colored impurities.

21. The yield is directly dependent upon the quality of the methyl acrylate used.

### 3. Methods of Preparation

Serine has been prepared by the Strecker method from glycolaldehyde<sup>1</sup> and from ethoxyacetaldehyde,<sup>2,3</sup> by the condensation of ethyl formate with ethyl hippurate followed by reduction and hydrolysis,<sup>4,5</sup> from the reaction product of chloromethyl ether with ethyl sodium phthalimidomalonate,<sup>6</sup> and by amination of  $\alpha$ -bromo- $\beta$ -methoxypropionic acid with subsequent demethylation.<sup>7</sup>

## SODIUM AMIDE



Submitted by F. W. BERGSTROM.

Checked by C. F. H. ALLEN and C. V. WILSON.

### 1. Procedure

THE apparatus is assembled as shown in Fig. 5. Ammonia gas from a commercial cylinder (Note 1) enters the system at K. R is a mercury trap which would serve as a safety valve if the system should become blocked by solidification of the amide owing to an accidental drop in temperature. J is a U-tube containing just enough mercury to seal the bend, and it serves to estimate the rate of ammonia flow. I is a Kjeldahl trap which prevents any mercury from being thrown into the fusion pot A, which (Note 2) is conveniently supported on a tripod set on bricks to raise it to a convenient height above the burner M. Through the cover of the fusion pot passes an outlet tube B, a thermometer well T, and the combined inlet tube CDE. The

<sup>1</sup> E. Fischer and Leuchs, *Ber.* **35**, 3788 (1902).

<sup>2</sup> Leuchs and Geiger, *ibid.* **39**, 2644 (1906).

<sup>3</sup> Dunn, Redemann, and Smith, *J. Biol. Chem.* **104**, 511 (1934).

<sup>4</sup> Erlenmeyer, *Ber.* **35**, 3769 (1902).

<sup>5</sup> Erlenmeyer and Stoop, *Ann.* **337**, 236 (1904).

<sup>6</sup> Mitra, *J. Indian Chem. Soc.* **7**, 799 (1930).

<sup>7</sup> Schlitz and Carter, *J. Biol. Chem.* **116**, 793 (1936).

thermometer well is welded shut at the bottom and projects about 6 mm. below the wider inlet tube, to which it is welded at the top. A gland or packed joint O, through which the inlet passes, is packed with a few turns of asbestos cord, the upper hexagonal nut being turned down with a wrench so that ammonia will not escape past the packing and so that there will be sufficient

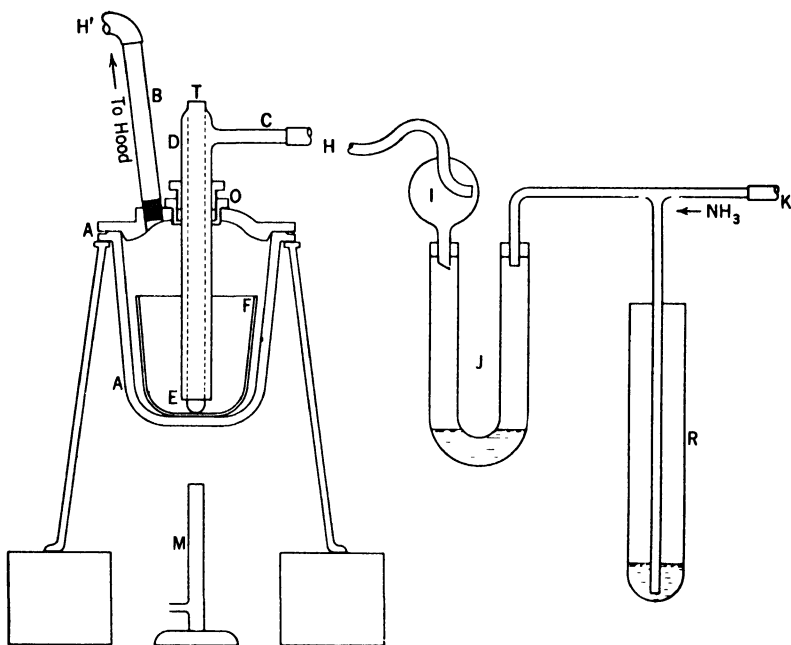


FIG. 5.

resistance to hold CDE in any position to which it may be raised (Note 3). The rubber tubes H, H' should be of sufficient length (5-7 cm.) to be very flexible and facilitate manipulation of the hot cover. The outlet tube B is at least 10 mm. in diameter.

At the outset of the run the pot A, with the thermometer well in the position shown in the diagram, is heated to about  $120^{\circ}$  for ten minutes in a slow stream of ammonia (Note 4). This serves to sweep the air and any traces of moisture from the system. The apparatus is then allowed to cool to  $70-80^{\circ}$ , the cover is removed, and a 250-cc. nickel crucible F is placed in the pot. The ammonia

inlet CDE is raised to just above the top of the nickel crucible, in which is then placed approximately 175 g. (7.6 gram atoms) of clean sodium (Note 5). The pot is now heated with the full flame of the burner; the sodium melts in five to ten minutes, whereupon the inlet tube CDE is pushed through the gland until it rests on the bottom of the crucible. When the temperature has reached  $320^{\circ}$ , the burner is turned down and adjusted to maintain the temperature at  $350\text{--}360^{\circ}$ . The ammonia flow is regulated so that the bubbles in J are just too rapid to count. After three and one-half to four hours (Notes 6 and 7), the temperature is lowered to about  $320^{\circ}$ , and the cover is lifted enough to see whether any unreacted metal remains; if none remains, the flame is removed and the crucible allowed to cool to  $230\text{--}240^{\circ}$ ; at this temperature the burner is replaced and heating continued for one-half hour to ensure removal of the bulk of the sodium hydride.

The burner is now extinguished, the ammonia shut off, and the pot cover removed by disconnecting at H, H'. The crucible is removed from the pot with tongs, and the molten amide is poured into a shallow iron tray, which has been previously heated to remove traces of moisture (Note 8). At this point it is essential to work rapidly to avoid solidification of the amide in the crucible (Note 9). As soon as the product has solidified sufficiently, the tray is transferred to a large desiccator to cool. When cold enough to handle, the tray is inverted on a clean heavy paper; the amide is removed by rapping the bottom of the pan and is at once transferred to convenient wide-mouthed bottles and covered with a petroleum fraction (Notes 10 and 11). The yields vary from 267 to 282 g. (90–95 per cent of the theoretical amount) (Notes 12, 13, and 14).

The sodium amide thus prepared is easily pulverized; it may be ground in a mortar under any hydrocarbon solvent. It is safer, though not necessary, where ether is to be used as a reaction medium, to grind the amide first under a hydrocarbon, the mixture being transferred to the reaction flask and then replaced by ether in the usual way (Notes 15, 16, and 17).

## 2. Notes

1. Ordinary commercial cylinders of ammonia are used; it is unnecessary to dry the gas.

2. The fusion pot is obtainable on the market from the Denver Fire Clay Company (cast-iron crucible and cover, one-quarter gallon, catalog No. 2136).

3. The gland O may be replaced by a sleeve or bushing and held in place by a set screw or by a clamp at any position desired.

4. Considerable time is saved by using a Meker or triple burner for raising the apparatus to reaction temperature, but an ordinary Tirrill burner is sufficient for the reaction.

5. The oxide coating or oil on commercial sodium should be removed before using. It is more convenient to use approximately 175 g. of sodium than to cut this exact amount.

6. The reaction time depends largely upon the rate at which the ammonia is admitted. If the current is too rapid there will be considerable splashing, and much of the molten amide will collect in the iron pot. Ordinarily the quantity of sodium specified will react completely in the time indicated. The total time for a run is slightly under six hours, of which not more than two to two and one-half hours of actual attention are required.

7. Any unreacted metal is easily visible as a globule, floating on the surface of the darker liquid. A flashlight aids in rapid inspection.

8. A pan 2 cm. high and 13 cm. in diameter is suitable for a run of this size. Any oxide coat should be removed by heating to redness, cooling, and polishing with emery paper; otherwise the product is deeply colored where it comes into contact with the pan. The same pan may be used repeatedly without further treatment other than cleaning and drying.

9. Some of the product invariably splashes out of the crucible onto the walls of the pot. If the quantity should be large (too rapid current of ammonia) it can be poured out, but if small it is chipped out after cooling.

10. Commercial "heptane" from petroleum, b.p. 90–100°, is

preferable, but other fractions may be used. A 750-cc. bottle will hold the product from one run.

11. Alternatively, the amide is allowed to cool completely in the nickel crucible in a slow current of ammonia and removed when cold. CDE is raised above the melt before cooling.

12. The chief variation in the yield is due to loss by splashing; it is difficult to remove the amide that has solidified on the walls of the iron pot. Some loss is accounted for by the sodium hydride carried away with the effluent gas.

13. Runs of other sizes may be made in the same apparatus. With half the quantity of sodium specified, temperature control demands much more attention. With larger quantities, the nickel crucible is dispensed with, and the carefully cleaned pot used. The checkers used 260–270 g. of sodium and averaged a yield of 94 per cent; the reaction time was increased by only one-half hour. By arranging two series of apparatus in parallel, but connected to the same cylinder of ammonia, one operator can prepare twice as much amide in almost the same time.

14. The color of the product is nearly white if the iron vessels are carefully cleaned but may be considerably on the gray side.

15. *Caution.* Sodium amide is a very reactive substance; it combines with oxygen and reacts explosively with water. The submitters recommended keeping the amide in sealed glass containers in an atmosphere of ammonia. The checkers preferred the use of petroleum fractions for greater convenience in handling; they have kept specimens under this solvent for three years without appreciable loss in activity.

When exposed to the atmosphere, sodium amide rapidly takes up moisture and carbon dioxide. When exposed to only limited amounts, as in imperfectly sealed containers, products are formed which render the resulting mixture highly explosive.<sup>1</sup> The formation of oxidation products is accompanied by the development of a yellow or brownish color. If such a change is noticed, the substance should be destroyed at once. This is conveniently accomplished by covering with much benzene, toluene, or kerosene and slowly adding dilute alcohol with stirring.

<sup>1</sup> Bergstrom and Fernelius, *Chem. Rev.* **12**, 43 (1933); **20**, 413 (1937).

16. After the preparation is completed, the cooled reactor should be dismantled and the parts immediately washed with alcohol, care being taken that all traces of sodium amide have been destroyed before water is brought into contact with any part of the equipment.

17. The submitters have prepared potassium amide in yields of 95 per cent in the same manner, but maintaining the temperature at 350–360° for the entire run. The apparatus should be rinsed with an alcohol-benzene mixture.

### 3. Methods of Preparation

Sodium amide has been prepared by the action of gaseous <sup>2</sup> or liquid <sup>3</sup> ammonia on sodium, by the action of ammonia on alloys of sodium,<sup>4</sup> and by the electrolysis of a solution of sodium cyanide <sup>5</sup> in liquid ammonia with a sodium amalgam electrode. A summary of the chemistry of alkali amides is given by Bergstrom and Fernelius.<sup>1</sup>

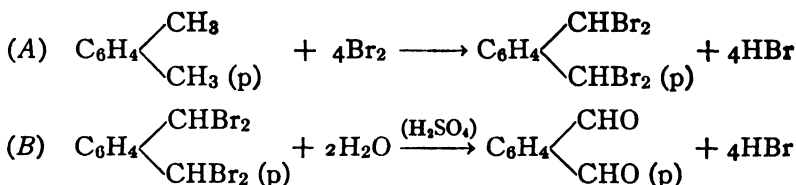
<sup>2</sup> Wislicenus, Ber. **25**, 2084 (1892); Titherly, J. Chem. Soc. **65**, 504 (1894); "Inorganic Syntheses," Vol I, p. 74, McGraw-Hill Book Company, Inc., New York, 1939; De Forcrand, Compt. rend **121**, 66 (1895); Dennis and Browne, J. Am. Chem. Soc. **26**, 587 (1904); Winter, ibid. **26**, 1484 (1904); Ruff and Geisel, Ber **39**, 828 (1906); Kraus and Cuy, J. Am. Chem. Soc **45**, 712 (1923); Guntz and Benoit, Bull. soc. chim. (4) **41**, 434 (1927); Fernelius and Bergstrom, J. Phys. Chem **35**, 740 (1931); Gilbert, Scott, Timmerli, and Hausley, Ind. Eng. Chem. **25**, 740 (1933); Shreve, Riechers, Rubenkoenig and Goodman, Ind. Eng. Chem **32**, 173 (1940)

<sup>3</sup> Joannis, Compt. rend. **112**, 392 (1891); McGee, J. Am. Chem. Soc. **43**, 586 (1921); Brit. pat. 222,718 (1923) [C. A. **19**, 1143 (1925)]; Vaughn, Vogt, and Nieuwland, J. Am. Chem. Soc. **56**, 2120 (1934).

<sup>4</sup> U. S. pat. 1,359,080 [C. A. **15**, 415 (1921)].

<sup>5</sup> Brit. pat. 222,718 (1923) [C. A. **19**, 1143 (1925)]; U. S. pat. 1,570,467 [C. A. **20**, 714 (1926)].

## TEREPHTHALDEHYDE



Submitted by J. M. SNELL and A. WEISSBERGER.

Checked by R. L. SHRINER and N. S. MOON.

## 1. Procedure

(A) *α,α,α',α'-Tetrabromo-*p*-xylene*.—A 1-l. three-necked flask is fitted with an oil-sealed mechanical stirrer, a 500-cc. dropping funnel, and a reflux condenser, the top of which is connected to a gas-absorption trap (Org. Syn. 14, 2). A 300-watt tungsten lamp is clamped in such a position that its bulb is within 1 in. of the flask (Note 1). Into the flask is introduced 100 g. (0.94 mole) of dry *p*-xylene (m.p. 11–12°), and the flask is heated in an oil bath maintained between 140° and 160°. The stirrer is started, and, when the xylene starts boiling, 700 g. (224 cc., 4.38 moles) of dry bromine (Note 2) is gradually added through the dropping funnel at such a rate that there is never any large amount of unreacted bromine in the flask. Stirring and heating are continued throughout the reaction, which requires six to ten hours. After all the bromine has reacted, the mixture is cooled and dissolved in 1 l. of warm chloroform. The chloroform solution is cooled in an ice bath and the product removed by filtration. It is light gray in color, melts at 165–169°, and weighs 250–258 g. After a second recrystallization from 1 l. of chloroform, 190–200 g. of light gray crystals melting at 168–170° is obtained. An additional 15–20 g. may be obtained by concentrating the chloroform filtrate to 250 cc. and recrystallizing the precipitate from fresh chloroform. The total yield is 205–220 g. (51–55 per cent of the theoretical amount).

(B) *Terephthalaldehyde*.—A 2-l. round-bottomed flask is fitted with a still-head, capillary ebullition tube, and receiver in an



assembly for a vacuum distillation. Into the flask are introduced 84.3 g. (0.2 mole) of finely powdered tetrabromo-*p*-xylene and 200 cc. of concentrated sulfuric acid (95 per cent). The reactants are thoroughly mixed by shaking. A vacuum is applied by means of a water pump, and a stream of air is allowed to pass through the capillary tube in order to facilitate the rapid removal of hydrogen bromide. The flask is heated in an oil bath to 70°, and, as the evolution of gas becomes less vigorous, the temperature of the bath is gradually raised to 110° (Note 3). The reaction is complete when a perfectly clear solution is obtained and no more gas is evolved (about two and one-half hours). The flask is then cooled and the contents are poured on 600 g. of crushed ice. The crystalline solid is collected on a filter, washed with a little water, and recrystallized from 600 cc. of 10 per cent methyl alcohol with the aid of 1 g. of decolorizing carbon to remove the yellow color. The small amount of tetrabromoxylene which remains undissolved is separated with the carbon and washed on the filter with two 100-cc. portions of hot 10 per cent methyl alcohol. The yield of pure product, m. p. 115–116°, is 21.7–22.5 g. (81–84 per cent of the theoretical amount).

## 2. Notes

1. It is important to have light shining on the reaction mixture throughout the bromination. The bromination may also be accomplished by placing the flask in direct sunlight.

2. The bromine is dried by shaking it with two 200-cc. portions of concentrated sulfuric acid.

3. The mixture foams considerably and must be watched. The foaming can be controlled by raising the temperature slowly and regulating the vacuum. For this reason it is difficult to hydrolyze larger amounts of the tetrabromide.

## 3. Methods of Preparation

Terephthaldehyde has been made by the action of lead nitrate on  $\alpha,\alpha'$ -dichloro-*p*-xylene<sup>1</sup> or  $\alpha,\alpha'$ -dibromo-*p*-xylene;<sup>2</sup> by

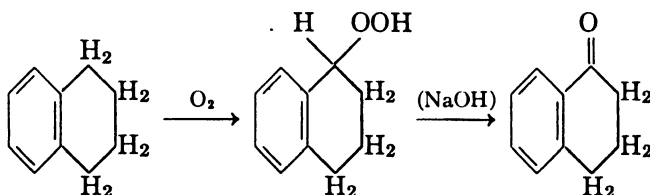
<sup>1</sup> Grimaux, Bull. soc. chim. (2) **25**, 337 (1876); Compt. rend. **83**, 825 (1877).

<sup>2</sup> Löw, Ann. **231**, 361 (1885).

the action of fuming nitric acid on dibromo-*p*-xylene;<sup>3</sup> by the hydrolysis of terephthaldehyde tetraacetate;<sup>4</sup> by the action of phosphorus pentachloride on *p*-xylyleneglycol monoethyl ether;<sup>5</sup> by the hydrolysis of  $\alpha,\alpha,\alpha',\alpha'$ -tetrachloro-*p*-xylene;<sup>6</sup> and by the hydrolysis of  $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*p*-xylene.<sup>7</sup> The method described here is essentially the modification described by Weissberger and Bach.<sup>8</sup>

### $\alpha$ -TETRALONE

(1,2)-Naphthalenone, 3,4-Dihydro-



Submitted by RALPH B. THOMPSON.

Checked by R. L. SHRINER and L. B. POLAND.

### 1. Procedure

FIVE HUNDRED grams of tetralin (3.78 moles) (Note 1) is placed in a 1-l. round-bottomed flask fitted with a thermometer, a tube extending to the bottom, and an efficient reflux condenser (Note 2). A slow stream of air is drawn through the tetralin by applying gentle suction from an aspirator pump to the end of the condenser. The air current is continued for fifty to fifty-five hours (Note 3) while the contents of the flask are maintained at 72–78° by means of a steam bath.

At the end of this period the partially oxidized tetralin is poured into 500 cc. of 2 *N* sodium hydroxide, with vigorous me-

<sup>3</sup> Löw, Ber. 18, 2072 (1885).

<sup>4</sup> Thiele and Winter, Ann. 311, 341 (1900).

<sup>5</sup> Colson, Bull. soc. chim. (2) 42, 152 (1884).

<sup>6</sup> Colson and Gautier, *ibid.* (2) 45, 506 (1886); Ann. chim. (6) 11, 25 (1887).

<sup>7</sup> Hönig, Monatsh. 9, 1150 (1888); Thiele and Gunther, Ann. 347, 106 (1906).

<sup>8</sup> Weissberger and Bach, Ber. 65, 24 (1932).

chanical stirring (Note 4). Stirring is continued and the mixture is heated on a steam bath to 60°; at this stage, cooling by adding ice may be necessary to hold the temperature below 70°. The mixture is cooled to room temperature and nearly neutralized with 6 *N* sulfuric acid (Note 5). The upper tetralin- $\alpha$ -tetralone layer is separated and washed with 100 cc. of 0.5 *N* sulfuric acid and then with 100 cc. of 1 per cent ferrous sulfate solution (Note 6). The mixture is dried with 25 g. of anhydrous sodium sulfate and fractionally distilled *in vacuo* through a packed column (Note 7). The unchanged tetralin distils at 65–72° at 2 mm. and amounts to 320–385 g. The temperature then rises, and the fraction boiling at 105–107° at 2 mm. (123–124° at 9 mm.) is practically pure  $\alpha$ -tetralone. The yield varies from 70 to 87 g. (44–56 per cent of the theoretical amount based on the tetralin not recovered).

## 2. Notes

1. Commercial tetralin with a boiling-point range of 206–209° was used.

2. A 65-cm. Liebig condenser surmounted by a 150-cm. Friedrich condenser was found to be satisfactory. A 100-cm. Liebig condenser may be used if the inner tube is packed with glass wool. The bubbler for the air should have 4–5 fine jets to provide a broken stream and fine bubbles.

3. Oxidation longer than fifty-five hours has no helpful effect; in some instances it has resulted in a reduced yield.

4. An alternative procedure for the isolation of  $\alpha$ -tetralone, which involves removal of the excess tetralin from the peroxide by vacuum distillation and subsequent treatment of the peroxide with alkali, is not recommended since heating of the peroxide may cause a violent explosion.

5. Keeping the solution basic prevents the extraction into the tetralin of acidic products which are highly colored; saturating the solution with sodium chloride makes the extraction more rapid.

6. If an emulsion forms at this stage, it may be broken by acidifying with sulfuric acid and adding 50 g. of sodium chloride.

The washing with ferrous sulfate is essential in order to destroy the last traces of peroxides.

7. The column packed with glass helices described by Whitmore and Lux<sup>1</sup> is quite satisfactory. A simple column which is

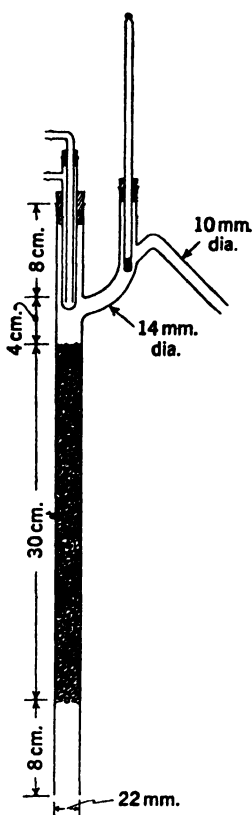


FIG. 6.

now available from the Corning Glass Company is shown in Fig. 6. This column may be packed with glass<sup>2</sup> or wire helices, Carborundum, or jack chain (Note 8). The body of the column is insulated by wrapping with asbestos paper. For high-boiling substances, the column should be heated by means of a winding of Nichrome resistance wire connected through an adjustable resistance. For fractionation of substances which boil very close together the packing should be glass or wire helices. In the present preparation and for ordinary work, a packing of Carborundum crystals the size of a grain of puffed wheat gives good separations in one distillation. These packed columns with reflux control have been shown to be very efficient.<sup>3</sup>

8. The glass helices may be purchased from the Scientific Glass Apparatus Company, Bloomfield, N. J., or the American Instrument Company, Silver Spring, Md.

Wire helices are readily made from No. 18 B. and S. gauge copper or Nichrome wire, by simultaneously winding two strands side by side on a  $\frac{1}{4}$ -in. steel mandrel. The spirals are cut into single helices by means of a thin emery wheel and then removed from the mandrel.

<sup>1</sup> Whitmore and Lux, J. Am. Chem. Soc. **54**, 3451 (1932).

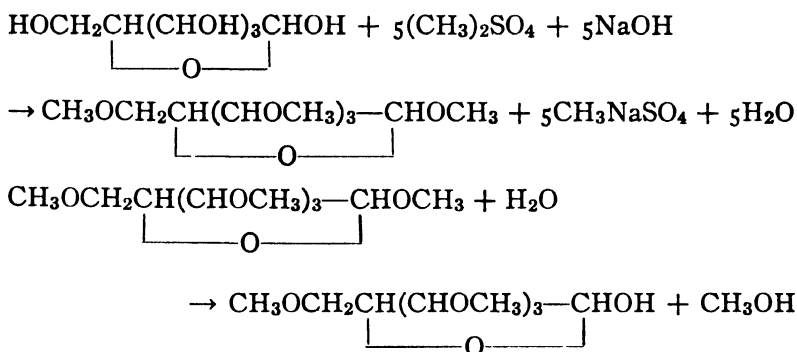
<sup>2</sup> Price and McDermott, Ind. Eng. Chem. Anal. Ed. **11**, 289 (1939).

<sup>3</sup> Fenske and co-workers, Ind. Eng. Chem. **24**, 408 (1932); **26**, 1169, 1213 (1934); **28**, 644 (1936).

### 3. Methods of Preparation

The method described is essentially that of Hock and Susemihl.<sup>4</sup> A similar procedure has appeared very recently.<sup>5</sup> Other methods of preparation have been reviewed in an earlier volume.<sup>6</sup>

#### 2,3,4,6-TETRAMETHYL-*d*-GLUCOSE



Submitted by EDWARD S. WEST and RAYMOND F. HOLDEN.

Checked by W. W. HARTMAN and A. J. SCHWADERER.

### 1. Procedure

THIS preparation must be carried out in a hood having good ventilation. Methyl sulfate has a high vapor pressure in spite of its high boiling point and is very poisonous. Ammonia is a specific antidote and should be kept on hand to destroy any of the ester accidentally spilled. It is advisable to wash the hands in dilute ammonium hydroxide frequently.

In a 2-l. distilling flask immersed in a 4-l. water bath are placed 25 g. (0.14 mole) of anhydrous glucose (Note 1) and 15 cc. of water. The flask is fitted with a cork through which passes a strong mechanical stirrer (Note 2) and a dropping tube con-

<sup>4</sup> Hock and Susemihl, Ber. **66**, 61 (1933).

<sup>5</sup> Brown, Widiger, and Letang, J. Am. Chem. Soc. **61**, 2601 (1939).

<sup>6</sup> Org. Syn. **15**, 77 (1935).

nected by rubber tubing and a screw clamp to a 500-cc. reservoir flask. The side tube of the flask is connected to a water condenser, fitted with a suction flask, from which fumes are led to a flue by a piece of tubing. The temperature of the water bath is raised to  $55^{\circ}$ , and the glucose is brought into solution with rapid stirring, which is maintained throughout the process. A mixture of 90 cc. (120 g., 9.5 moles) of methyl sulfate and 125 cc. of carbon tetrachloride is added from the reservoir as quickly as possible to the flask. The clamp is closed, and 400 cc. (580 g.) of 40 per cent (by weight) sodium hydroxide is placed in the reservoir. The alkali is admitted to the flask at the rate of one drop in two seconds for five minutes, then one drop per second for five minutes, and then three drops per second until the distillation of carbon tetrachloride slackens or ceases. This is usually accomplished in fifteen to twenty minutes and after the addition of 70-90 cc. of alkali. The heat of reaction generally maintains the proper temperature of  $50-55^{\circ}$  throughout this stage without the necessity of heating the water bath externally. The remainder of the alkali is added as quickly as possible, and the bath temperature raised to and maintained at  $70-75^{\circ}$ . Then 160 cc. (208 g., 1.65 moles) of methyl sulfate is placed in the reservoir immediately and added at the rate of three to four drops per second (slower if the mixture foams seriously).

After all the methyl sulfate has been added, the bath is boiled for thirty minutes with continued stirring. The contents of the flask are cooled, diluted with sufficient water to dissolve most of the separated sodium sulfate, and extracted four times with 150-cc. portions of chloroform; the chloroform and water layers are separated carefully. The combined chloroform extracts (Note 3) are placed in a 2- or 3-l. distilling flask (with condenser attached) with 400 cc. of 2 *N* hydrochloric acid, and the chloroform is removed by distillation. A rapid current of steam is then passed through the solution for one hour, care being taken to maintain the volume approximately constant by heating the flask. Five grams of Norite is added to the hot solution, which is then cooled and filtered. The filtrate is saturated with sodium sulfate and extracted four times with 150-cc. portions of chloro-

form. The combined chloroform extracts are dried with sodium sulfate, 1 g. of Norite is added, and the mixture is filtered. The chloroform is removed as completely as possible in a boiling water bath without vacuum and finally at the water pump. The heavy syrup is treated with 40–50 cc. of petroleum ether (30–60°) and shaken for a short time, whereupon it sets to a mass of crystals. After cooling in an ice bath for one-half hour, the crystals are filtered, washed with a little cold petroleum ether, and dried over calcium chloride *in vacuo*. The yield is 15–18 g. (46–55 per cent of the theoretical amount) (Note 3). The specific rotation,  $[\alpha]_D^{26}$ , in water was found to be about +79–79.5°, when  $c = 4$ ; a drop of 15 per cent ammonia was added to speed equilibration, and the readings were made one hour after the solution was prepared in a 2-dm. tube.

The slightly impure product is recrystallized from petroleum ether (b.p. 30–60°) containing 0.5 per cent of anhydrous ether in a continuous extractor, using 100 cc. of solvent per 6–7 g. of compound. One crystallization is generally sufficient to give a pure product. The specific rotation of pure tetramethyl-*d*-glucose prepared by this method is approximately  $[\alpha]_D^{21} + 81.3^\circ$  (Note 4).

## 2. Notes

1.  $\alpha$ -Methylglucoside may be methylated in the same way as glucose, using four-fifths of the reagents and hydrolyzing the tetramethyl- $\alpha$ -methylglucoside (contained in the chloroform solution) for three hours instead of the one hour required for the mixture of  $\alpha$ - and  $\beta$ -tetramethylmethylglucosides obtained directly from glucose. Tetramethylglucose prepared in this way may show the correct rotation without recrystallization.

2. The stirrer consists of a  $\frac{3}{16}$ -in. Monel rod formed into a 1-in. flattened loop at one end for stirring. The stirrer is passed through a closely fitting  $\frac{3}{8}$  by 5 in. brass bearing with a packing nut at the lower end, the top of the bearing being countersunk to facilitate oiling with heavy engine oil. This metal stirrer permits much more vigorous stirring (which is essential) than the ordinary glass apparatus.

3. The tetramethylmethylglucosides may be isolated from the chloroform solution by drying with sodium sulfate, distilling off the chloroform, and then vacuum-distilling the syrup. The distillation can be easily carried out in a distilling flask (100-cc.) filled with glass wool (which effectively prevents bumping) and having a low side arm. The glass wool materially lowers the distilling temperature. The mixture of  $\alpha$ - and  $\beta$ -glucosides (approximately 85 per cent  $\beta$  form) and the pure  $\alpha$  form distil at about 88–90° at 0.15 mm. under the above conditions, and they constitute the entire distillate after the solvent has been removed. The specific rotation,  $[\alpha]_D$ , lies between +9° and +12°, depending upon the proportion of isomers in the distillate; for the pure  $\alpha$  form it is 151° at 25°. The refractive index is 1.4445<sub>D</sub><sup>20°</sup> for the  $\alpha, \beta$  mixture and 1.4460<sub>D</sub><sup>20°</sup> for the pure  $\alpha$  isomer.

4. The correct value for any temperature between 5° and 37° may be calculated from the equation  $[\alpha]_D^T = 85 - 0.1846t$ . The melting point of the compound varies according to the proportion of  $\alpha$  and  $\beta$  isomers present. After prolonged digestion with petroleum ether, the  $\alpha$  isomer predominates and the melting point rises. A sample of the product recrystallized once melted at 90–93°, and after five recrystallizations it melted at 98°, without change in the optical rotation.

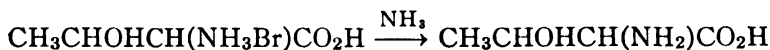
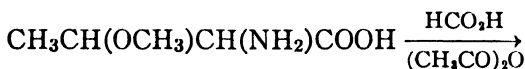
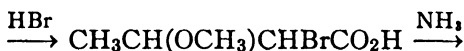
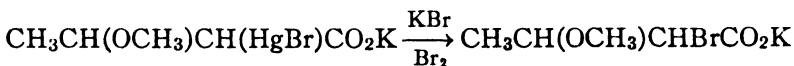
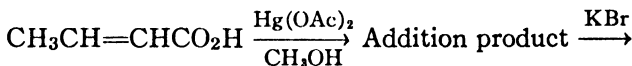
### 3. Methods of Preparation

Tetramethyl-*d*-glucose has been prepared by the action of methyl iodide and silver oxide on methylglucoside,<sup>1</sup> by the action of methyl sulfate and alkali on both methylglucoside and glucose,<sup>2</sup> and also by hydrolysis of various methylated polysaccharides.

<sup>1</sup> Purdie and Irvine, J. Chem. Soc. 83, 1021 (1903).

<sup>2</sup> Haworth, J. Chem. Soc. 107, 8 (1915); 113, 188 (1918).



**dl-THREONINE**

Submitted by HERBERT E. CARTER and HAROLD D. WEST.

Checked by NATHAN L. DRAKE and WILLIAM A. STANTON.

**1. Procedure**

(A) *α-Bromo-β-methoxy-n-butyric Acid*.—In a 5-l. flask are placed 3 l. of methyl alcohol, 640 g. (2 moles) of mercuric acetate (Note 1), and 172 g. (2 moles) of crotonic acid (Note 2). The flask is warmed on a steam cone and shaken vigorously until the mercuric acetate dissolves (about ten minutes). The solution is allowed to stand at room temperature for forty-eight hours (Note 3), then the precipitate is filtered, washed twice with 300-cc. portions of methyl alcohol, and air-dried. The yield is 625–650 g. (Note 4). This material is powdered and dissolved in a solution of 360 g. (3 moles) of potassium bromide in 2 l. of water, and the solution is placed in a 4-l. beaker, which is cooled in an ice bath and exposed to direct sunlight (Note 5). A solution of 320 g. (2 moles) of bromine and 360 g. (3 moles) of potassium bromide in 600 cc. of water is added with stirring during twenty to forty minutes, avoiding a large excess of bromine. After ten to fifteen minutes' standing, any excess bromine is destroyed with sodium bisulfite. The bromo acids are isolated as follows: The solution is extracted once with 300 cc. of ether to

remove a small amount of lachrymatory material and, after acidification with 400 cc. of 40 per cent hydrobromic acid, is extracted again with six 800-cc. portions of ether. The ether extracts are combined, washed once with a small volume of cold water, and dried over anhydrous sodium sulfate. The ether is removed by distillation, leaving the crude bromo acid mixture.

The yield of crude bromo acids is 350–370 g. (88–93 per cent of the theoretical amount based on the crotonic acid used in the first step). This material is used without purification in the preparation of aminomethoxybutyric acid.

The crude bromo acids may be freed from impurities by fractionation under reduced pressure. The fraction distilling below  $125^{\circ}$  at 10 mm. ( $105^{\circ}/3$  mm.) is discarded; the remainder distills at  $125$ – $128^{\circ}$  at 10 mm. ( $105$ – $107^{\circ}/3$  mm.) and consists of a mixture of stereoisomeric acids. The yield is 75–85 per cent of the theoretical amount based on the crotonic acid used in the first step.

(B) *dl*-Threonine.—One hundred and seventy-five grams of crude bromomethoxybutyric acid is heated with 2 l. of concentrated ammonium hydroxide for six hours at  $90$ – $100^{\circ}$  in a glass-lined autoclave (p. 85) (Note 6). The solution is concentrated to a thick gum under reduced pressure (Note 7), water is added, and the solution is reconcentrated under reduced pressure. The residue is allowed to stand under acetone with frequent shaking (Note 8) until the material has crystallized completely (one or two days). The acetone is decanted, and the residue dissolved in 1 l. of 85–90 per cent formic acid (Note 9). The solution is warmed to  $45^{\circ}$ , and 350 g. (330 cc.) of acetic anhydride is added with stirring during ten minutes. The heat of reaction causes the temperature of the solution to rise to  $70$ – $80^{\circ}$ , and the temperature of the mixture is maintained within this range for about fifteen minutes. The solution is next evaporated to dryness under reduced pressure. The residue is dissolved, while being warmed on the steam bath, in the minimum amount of water (Note 10), and the solution is cooled overnight in the icebox. The crystals are filtered and air-dried. This material is a mixture of formyl derivatives (Note 11). One recrystallization from 150 cc.

of hot water yields about 25 g. of practically pure formyl-*dl*-O-methylthreonine melting at 174–176°. An additional 3–5 g. is obtained by working up the filtrates. The yield is 25 per cent of the theoretical amount (Note 12).

Twenty-five grams (0.16 mole) of formyl-*dl*-O-methylthreonine is refluxed for two hours with 360 cc. of constant-boiling hydrobromic acid. The solution is concentrated under reduced pressure (Note 13). Sufficient water is added to dissolve all the residue, and the solution is reconcentrated under reduced pressure. The gummy residue is next dissolved in 450 cc. of absolute alcohol, and concentrated ammonium hydroxide is added until the odor of ammonia persists after vigorous shaking. The solution is cooled in the icebox overnight, and the crystals are filtered and dissolved in 3 volumes of hot water (about 5 cc. of water per gram of crude material). Seven volumes of absolute alcohol are added, and the solution is cooled to room temperature with scratching of the flask to induce crystallization. It is then cooled in an icebox overnight. The crystals are filtered and washed twice with 90-cc. portions of absolute alcohol and once with ether. The yield is 18–20 g. (85–90 per cent of the theoretical amount based on the formyl-*dl*-O-methylthreonine) of pure *dl*-threonine, melting with decomposition at 234–235° (Note 14).

## 2. Notes

1. The mercuric acetate may be replaced by equivalent amounts of mercuric oxide and glacial acetic acid.

2. The crotonic acid was obtained from the Niacet Chemical Company and used without purification.

3. It is advisable to scratch the flask with a glass rod after three or four hours. This usually initiates precipitation of the addition product in a finely divided form. If this is not done, the addition product may crystallize slowly on the sides of the flask in a cake which is removed only with the greatest difficulty. It is also advantageous to stir the mixture mechanically for several hours after crystallization begins in order to prevent caking.

4. The exact yield cannot be calculated, since the structure of

the addition product is unknown. The yield is almost quantitative, however, since only a small amount of mercury remains in the filtrate.

5. The bromination can be carried out equally successfully under the illumination of two No. 2 Photoflood lamps in suitable reflectors placed directly above the surface of the liquid. Under these conditions, however, the addition of the bromine requires ten to fifteen minutes longer.

6. According to the submitters the amination can be carried out in ordinary 500-cc. glass bottles if the temperature does not exceed 85°. The time of heating should then be extended to eight to ten hours.

7. All the concentrations under reduced pressure required in this preparation may be carried out at the pressure provided by an efficient water pump.

8. The material, if allowed to stand without shaking, solidifies to a hard cake. The shaking furthers extraction of certain gummy impurities which interfere with the separation to be carried out later.

9. If a mixture of *dl*-threonine and *dl*-allothreonine is desired instead of *dl*-threonine alone, the residue may be dissolved directly in 1200 cc. of 48 per cent hydrobromic acid and refluxed for two hours. After removal of the hydrobromic acid under reduced pressure, the gummy residue is dissolved in warm water, and concentrated ammonium hydroxide is added slowly until a faint odor of ammonia persists after vigorous shaking. The solution is concentrated until crystals appear, and 3-4 volumes of alcohol is added. The acids are recrystallized by dissolving in the minimum amount of hot water (4-5 cc. per gram) and adding 4-5 volumes of alcohol. The solution is allowed to cool and permitted to stand overnight at room temperature.

10. If, after solution is complete on the steam bath, 10 per cent more water is added, the quality of the product is better, but the yield is slightly less.

11. Formyl-*dl*-*O*-methylthreonine melts at 173-174°. Formyl-*dl*-*O*-methylallothreonine melts at 152-153°.

12. Crude *dl*-allothreonine may be obtained from the mother

liquors by concentrating them to dryness, refluxing the residue with 10 volumes of 48 per cent hydrobromic acid, and working up the solution as described for *dl*-threonine. The product contains a small amount of *dl*-threonine which can be largely removed by three or four recrystallizations from 50 per cent alcohol. *dl*-Allothreonine of this purity melts at 242–243°.

13. Constant-boiling hydrobromic acid can be recovered by fractionating the distillate at atmospheric pressure.

14. The melting points obtained by the checkers were consistently three to four degrees above those given. The melting points of these compounds vary with the method of determination.

### 3. Methods of Preparation

$\alpha$ -Amino- $\beta$ -hydroxybutyric acid has been prepared by a procedure similar to the one described, using ethyl crotonate as the starting material.<sup>1</sup> A mixture of the  $\alpha$ -amino- $\beta$ -hydroxy- and  $\alpha$ -hydroxy- $\beta$ -aminobutyric acids has been secured by treating crotonic acid with hypochlorous acid and heating the resulting product with dry ammonia under pressure.<sup>2</sup> A mixture containing threonine has been obtained by treatment of acetoacetic ester with sodium nitrite and acetic acid; the resultant ethyl oximinoacetoacetate was then converted by means of diethyl sulfate into ethyl *O*-ethyloximinoacetoacetate. This product was reduced by hydrogen and Raney nickel to an impure ethyl  $\alpha$ -amino- $\beta$ -hydroxybutyrate, which was then hydrolyzed to a mixture of *dl*-threonine and *dl*-allothreonine.<sup>3</sup> The method described is one which recently appeared in the literature.<sup>4</sup> According to a recent paper<sup>5</sup> the *dl*-allothreonine may be converted into *dl*-threonine.

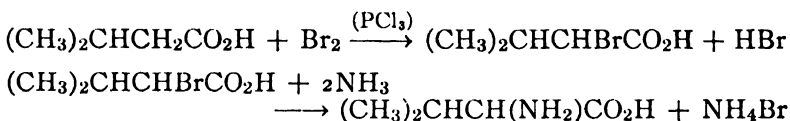
<sup>1</sup> Abderhalden and Heyns, Ber. **67**, 530 (1934).

<sup>2</sup> Burch, J. Chem. Soc. **137**, 310 (1930).

<sup>3</sup> Adkins and Reeve, J. Am. Chem. Soc. **60**, 1330 (1938).

<sup>4</sup> West and Carter, J. Biol. Chem. **119**, 109 (1937).

<sup>5</sup> Carter, Handler, and Melville, *ibid.* **129**, 362 (1939).

***dl*-VALINE****(Isovaleric Acid,  $\alpha$ -Amino)**

Submitted by C. S. MARVEL.\*

Checked by C. F. H. ALLEN and J. VAN ALLAN.

**1. Procedure**

(A)  *$\alpha$ -Bromoisovaleric Acid*.—One kilogram of commercial *i*-valeric acid monohydrate is placed in a 3-l. round-bottomed flask together with 500 cc. of benzene. The water and benzene are distilled, using a short column, until the temperature of the vapor reaches 100°. The temperature rises rapidly when the benzene is removed. The residue is cooled and 878 g. (934 cc., 8.6 moles) of it is placed in a 3-l. round-bottomed flask fitted with a long reflux condenser. The top of the condenser is connected by glass tubing to an empty 500-cc. Erlenmeyer flask which acts as a safety trap. A second outlet on the Erlenmeyer flask connects to a gas-absorption trap (Note 1). Fifteen hundred grams (480 cc.) of dry bromine (Note 2) is added to the acid, and then 15 cc. of phosphorus trichloride is added through the top of the condenser.

The mixture is heated on an oil bath at 70–80° for ten to twenty hours or until the condenser no longer shows the deep red color of bromine. Another 25-cc. portion of bromine is added and the flask heated as before. When the color has again disappeared, the temperature of the bath is slowly raised to 100–105° and maintained there for one and one-half to two hours.

The crude bromo acid is placed in a 2-l. modified Claisen flask and distilled under reduced pressure. The low-boiling

\* These directions are the result of the efforts of a large number of men who have worked on the preparation of valine at the University of Illinois during the past twenty years.

fraction is mainly unbrominated acid (Note 3). The fraction boiling at 110–125° at 15 mm. is collected. The yield is 1364–1380 g. (87.5–88.6 per cent of the theoretical amount).

(B) *dl-Valine*.—To 2 l. of technical ammonium hydroxide (sp. gr. 0.90) in a 3-l. round-bottomed flask is added 330 g. (1.82 moles) of  $\alpha$ -bromoisovaleric acid. A stopper is wired in and the flask allowed to stand at room temperature for a week. The contents from three such amination flasks are combined in a 12-l. flask and the ammonia removed by heating on the steam cone overnight. The solution is then concentrated to a thin paste (about 800 cc.) by means of a water pump (Note 4). The solid material is collected on a filter and, when dry, amounts to 470 g. This is recrystallized by dissolving in 2400 cc. of water heated to 95° on a steam cone, treating with 10 g. of Norite for thirty minutes, filtering hot, adding an equal volume of 95 per cent alcohol, and cooling overnight in the icebox. The valine is collected on a filter and washed with 150 cc. of cold absolute alcohol. The yield is 200–235 g. A second crop is obtained by evaporating the filtrate from the recrystallization on the water pump until crystals form, adding an equal volume of 95 per cent alcohol, and cooling as before. The amino acid obtained in this way amounts to 34 g.

The second filtrate from the recrystallization together with the filtrate from the original concentration is evaporated to dryness and extracted with 500 cc. of glacial acetic acid on a steam cone. The inorganic salts are filtered and the acetic acid is removed by distillation under reduced pressure. One liter of water is added, and it, too, is removed by distillation under reduced pressure. This operation is repeated. These three distillations require one day. The residue is dissolved in the minimum amount of hot water (about 300 cc.). The solution is then treated with Norite as before and filtered hot, and an equal volume of 95 per cent alcohol is added. The yield on cooling overnight in the icebox is 34 g. An additional 8 g. can be obtained from the mother liquor by concentration and addition of alcohol as was done with the original mother liquor. The total yield of valine is 300–311 g. (47–48 per cent of the theoretical amount),

which decomposes at 280–282° in a sealed capillary (Notes 5 and 6).

## 2. Notes

1. The hydrogen bromide may be absorbed in water and constant-boiling hydrobromic acid formed (Org. Syn. Coll. Vol. 1, 23).

2. The bromine is dried by shaking with 1 l. of concentrated sulfuric acid.

3. The low-boiling fraction (56–80 g.) may be combined with the next portion of acid to be brominated, or several such fractions are collected and brominated together. In this latter case, only three-fifths as much bromine is used as in the original run.

4. This condition is attained when 1850–1950 cc. of distillate has been collected (five hours).

5. The quantities stated for each fraction are approximate. If separations are incomplete, the melting point will be 275–280°.

6. Valine prepared in this manner has the calculated amino nitrogen content.

## 3. Methods of Preparation

Valine has been prepared by the action of alcoholic ammonia on  $\alpha$ -chloroisovaleric acid;<sup>1</sup> by the action of aqueous ammonia on  $\alpha$ -bromoisovaleric acid;<sup>2</sup> by the action of ammonia and ammonium carbonate on  $\alpha$ -bromoisovaleric acid;<sup>3</sup> by heating iso-propyl-malonylazidic acid and subsequent hydrolysis;<sup>4</sup> by the action of ammonia and hydrogen cyanide on isobutyraldehyde followed by hydrolysis.<sup>5</sup>  $\alpha$ -Bromoisovaleric acid has been prepared in several ways as described in an earlier volume.<sup>6</sup>

<sup>1</sup> Schlebusch, Ann. **141**, 326 (1867).

<sup>2</sup> Clark and Fittig, Ann. **139**, 202 (1866); Schmidt and Sachtleben, *ibid.* **193**, 105 (1878).

<sup>3</sup> Slimmer, Ber. **35**, 401 (1902).

<sup>4</sup> Curtius, J. prakt. Chem. **125**, 228 (1930).

<sup>5</sup> Lipp, Ann. **205**, 18 (1880).

<sup>6</sup> Org. Syn. **11**, 22.



# SUBJECT INDEX

(This Index Comprises Material from Volume 20 only.)

Names in capital letters refer to titles of individual preparations. Numbers in italics refer to preparative directions for substances formed either as principal products or as by-products; numbers in ordinary type indicate pages on which compounds or subjects are mentioned in connection with other preparations. For example, ACETONE CYANOHYDRIN, 42, 43, indicates that acetone cyanohydrin is mentioned on page 42 and that directions for its preparation are given in detail on page 43.

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